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Modulating the Reactivity of Heterocyclic Ketene Aminals in MCR: Selective Construction of Tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridines

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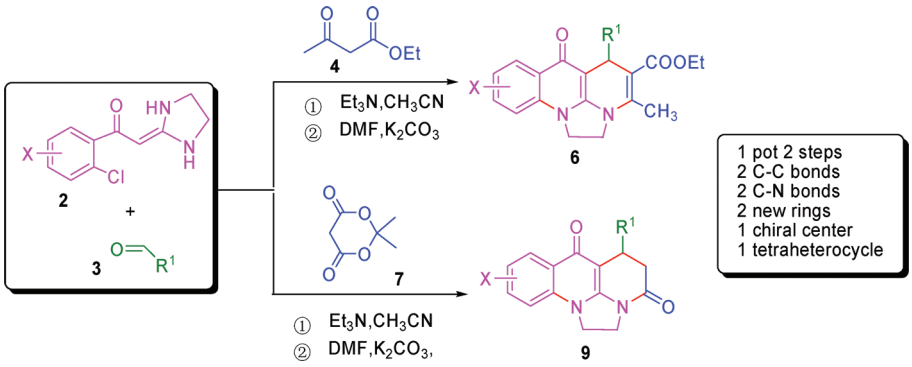

Two new kinds of tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridine derivatives have been successfully synthesized by cascade reactions including Knoevenagel condensation, aza-ene reaction, imine−enamine tautomerization, cyclocondensation, and intramolecular S_NAr of precursors 2-(2-chloroaroyl)methylene-imidazolidines with aromatic aldehydes and ethyl acetoacetate or Meldrum's acid under mild conditions, respectively. These studies highlighted the concept of a substrate-design approach to the development of novel multicomponent reactions by simply incorporating an *o*-halo group into the aryl ring of 2-benzoyl-methyleneimidazolidine as new synthons. In this domino reaction, at least six different active sites are involved; two C−C bonds, two C−N bonds, and two new rings are constructed with all reactants efficiently utilized in the chemical transformation.

Introduction

Carbon−carbon and carbon−heteroatom bond-forming reactions are central to organic synthesis. The synthesis of heterocycles often involves ene reaction.[1] Due to its synthetic potential in organic chemistry, the ene reaction has received much attention, and great development has been achieved particularly in the past three decades.[2] Meanwhile, multicomponent coupling reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from multifunctional substrates that react sequentially in an intramolecular fashion. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis.[3]

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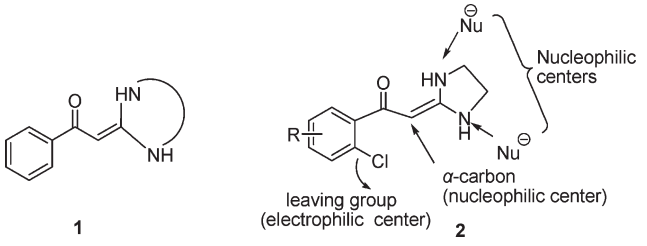

FIGURE 1. Functionalized ketene acetals.

Heterocyclic ketene aminals (HKAs) are powerful and versatile intermediates in heterocyclic synthesis. Reactions of cyclic ketene aminals of the general formula **1** with a number of biselectrophilic reagents such as β-keto ester enol tosylates,[4] propiolic acid ester,[5] aryl azides,[6] polyhaloisophthalonitrile,[7] Meldrum's acid and aldehydes,[8] bis(methylthio)methylene malononitrile,[9] itaconic anhydride,[10] α-bromo ketones,[11] ethyl 2-(bromomethyl)benzoate,[12] Baylis−Hillman acetates,[13] diethyl azodicarboxylate,[14] and 1,3-dibromopropane[15] have been successfully used to give five- and six-membered and fused heterocycles during the past years. 2-(2-Chloroaroyl)methyleneimidazolidines **2** (Figure 1), as new heterocyclic ketene aminals (HKAs), show structural features such as the highly polarized push−pull interaction C═C double bond and use of Cl atom as leaving group. On one hand, because of the conjugation effect of the electron-donating amino groups and electron-withdrawing carbonyl group, the nucleophilicity at the α carbon is greater than the nitrogen atoms. On the other hand, by simply incorporating an *o*-halo group into the aryl ring of 2-benzoylmethyleneimidazolidine, novel heterocyclic ketene aminals **2** would subject to an intramolecular nucleophilic aryl substitution reaction by attack of nitrogen atom. Therefore, precursors **2** display a different reactivity profile to that of 2-benzoylmethyleneimidazolidine **1** and could be developed a new strategy for the synthesis of an unusual tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*]-[1,8]naphthyridine derivatives.

Functionalized naphthyridines represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. More than 1000 patents were located claiming potential pharmaceutical applications,[16] such as antibacterial,[17] anti-HIV,[18] antischizophrenia,[19] antiasthma,[20] anti-inflammatory,[21] antihypertensive,[22] and anticancer[23] activities. Therefore, the synthesis of tetrahydroimidazo[3,2,1-*ij*][1,8]naphthyridine derivatives may be of great significance. To the best of our knowledge, very few molecules of tetrahydroimidazo[3,2,1-*ij*][1,8]naphthyridines have been synthesized, and there is no general strategy to prepare them.[24] In contrast to these previous approaches which lack scope and flexibility, our serendipitous route to this class of heterocyclic system is efficient and fairly general.

On the basis of our progressive endeavors in exploring novel and practical multicomponent reactions to synthesize useful heterocyclic compounds,[25] by simply incorporating an *o*-halo group into the aryl ring of 2-benzoylmethyleneimidazolidine we could develop two new three-component cascade reactions for the selective synthesis of tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*]-[1,8]naphthyridine derivatives with 2-(2-chloroaroyl)methyleneimidazolidines **2**, aldehydes **3**, and ethyl acetoacetate **4** or Meldrum's acid **7**.

Results and Discussion

Aza-ene reaction and nucleophilic substitution are two major reactions in organic chemistry. In the initial experiment, we explored the three-component aza-ene-type reaction of novel heterocyclic ketene aminal, 2-(2,4-dichlorobenzoyl)-methylene imidazolidine **2a**, with benzaldehyde **3a** and ethyl acetoacetate **4** as the model substrates for the optimization of the reaction conditions, such as different solvents, molar ratios, and catalysts (the results are summarized in Table S1, Supporting Information). It was clear from the experiments that the best conditions could be the use of a molar ratio of 1:1.2:1.2 of **2a**:**3a**:**4**, Et_3N (0.4 equiv) as base and MeCN as solvent at 81 °C.

The subsequent S_NAr cyclization requires a suitable base to enhance the nucleophilicity of the nitrogen atom of imidazole ring by the capture of HCl during the reaction. Then, we

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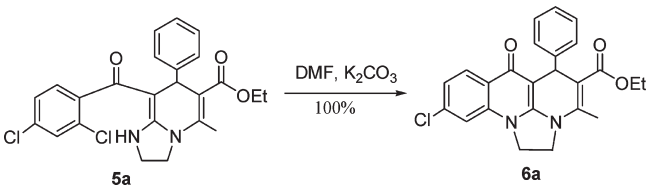
SCHEME 1. Conversion of 5a to 6a in the Presence of K_2CO_3



directly explored the use of **5a** in the presence of K_2CO_3 in DMF at 100 °C for about 12 h monitoring by TLC (Scheme 1). To our surprise, the reaction conditions did not require any optimization, and led to the formation of the corresponding ethyl 10-chloro-4-methyl-7-oxo-6-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*] [1,8]naphthyridine-5-carboxylate **6a** in almost quantitative yield.

Encouraged by the efficiency of the two consecutive domino processes of the aza-ene reaction and nucleophilic substitution, we set out to explore reaction conditions that would enable its combination with three-component synthesis of tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridines **6** in a one-pot procedure. We performed aza-ene-type reaction of 2-(2,4-dichlorophenyl)methyleneimidazolidine **2a** with benzaldehyde **3a** and ethyl acetoacetate **4** by simply combining three components in MeCN employing a molar ratio of 1:1.2:1.2 and Et_3N as base. Stirring the mixture at 81 °C for 8 h readily gave the expected aza-ene-type adduct **5a**, which was not isolated. After removal of the solvent, the residue was mixed with 1 equiv of K_2CO_3 in DMF, and the mixture was heated to 100 °C for 12 h. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature, and an amount of ice−water was added to precipitate the product which was then collected by filtration and washed with cool water. The dry solid was then washed with ethanol to afford the expected product **6a** in 87% yield (Table 1, entry 1).

Under the above optimized conditions, the scope of this new MCR process was next examined using **2a** other 11 aromatic aldehydes **3b**−**l** and ethyl acetoacetate **4** (Table 1, entries 2−12). The results demonstrated that the reactions went smoothly, and the yields were all satisfactory. To further expand the scope of 2-(2-chloroaroyl) methyleneimidazolidine substrates, we used 2-(2,5-dichlorobenzoyl)methyleneimidazolidine **2b**, 2-(2,4-dichloro-5-fluorobenzoyl)methyleneimidazolidine **2c**, and 2-(2-chlorobenzoyl)methyleneimidazolidine **2d** instead of **2a** in this process (Table 1, entries 13−15). As can be seen from Table 2, when aryl aldehydes bearing either electron-donating or electron-withdrawing groups were used as the substrates, the reactions could proceed successfully, and the corresponding products **6** were obtained in excellent yields. That is, the electronic effects of the substituents on the aromatic ring have no significant influence on the reaction yields. Compared to **6m** and **6o**, for example, the yields of **6a** and **6n** are slightly higher and the reaction time is slightly shorter, which might be attributed to the presence and the site of R (R = Cl) on the aromatic ring. A 4-chloro group *meta* to 2-chloro in **2a** and **2c** only gives an inductive effect with a strong electron-withdrawing group leading to an increase of electropositivity of C_2, whereas a 5-chloro group *para* to 2-chloro in **2b** gives both inductive and conjugate effects leading to a decrease of electropositivity of C_2, so the 2-chloro group is more easily removed in **2a** and **2c** as compared to **2b** and **2d** during the nucleophilic aromatic substitution reaction.

The structural determinations of all products **6a**−**o** were achieved following their analytical and spectral data. Importantly, this reaction generates one chiral center, but only one isomer was observed through ^{1}H NMR and ^{13}C NMR spectra, thin-layer chromatography, and X-ray diffraction analysis of product **6a** (see the Supporting Information).

It is noteworthy that all of the isolated products need only washing with ethanol rather than column chromatography or recrystallization. This easy purification makes this methodology facile, practical, and rapid to execute. Significantly, in this operationally simple domino reaction, at least six different reactive sites are involved; two C−C bonds, two C−N bonds, and two new rings are constructed with all reactants utilized in the chemical transformation. Therefore, this domino reaction can be extensively employed as an excellent method for the synthesis of tetrahydrobenzo-[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridine derivatives.

Next, we used Meldrum's acid **7** instead of ethyl acetoacetate **4** in this process. Meldrum's acid (2,2-dimethyl-1, 3-dioxane-4,6-dione)[26] as a class of acylal is a widely useful methyl derivative.[27] It is remarkably acidic (pK_a 7.3 in DMSO at 25 °C) compared to the related dicarbonyl compounds.[28] The high value for C−H acidity and exceptional behavior have made it an important candidate for the design of new practical and facile domino reactions in organic synthesis.[29] Yu and Huang et al.[8] reported a novel one-pot reaction involving HKAs, Meldrum's acid, and aldehydes to synthesize tetrahydropyridinone-fused 1,3-diazaheterocycles. However, to the best of our knowledge, the benzo[*b*]imidazo-[3,2,1-*ij*][1,8]naphthyridines have not been reported before using 2-(2-chloroaroyl)methyleneimidazolidines **2** as novel *N, N*-ketene acetal precursors. Our strategy assumes that precursors **2** might react with Meldrum's acid and aldehydes to set up new annulation on the basis of the aza-ene reaction and nucleophilic substitution.

The above optimized conditions were applied to the reaction of **2a** with 4-bromobenzaldehyde **3b** and Meldrum's acid **7**. Stirring the mixture at 81 °C for about 8 h gave the aza-ene intermediate, which was not separated, followed by evaporation of the solvent and subsequent addition of K_2CO_3 in DMF for about 12 h. Unfortunately, compared with the MCR of **2a**, aromatic aldehydes **3**, and ethyl acetoacetate **4**, a significant difference was that 6-(4-bromophenyl)-10-chloro-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione **9b** was found as a major product along with the formation of a small amount of unidentified byproduct (**9′b**, 17% yield, which may be oxidation product, it was identified from a singlet at δ 5.96 ppm assigned to the olefinic proton of pyridone moiety). When improving the purity of **9b**, we found that when the reaction time was shortened from 12 to 3 h, the yield of unidentified byproduct decreased to 2%. To our satisfaction, treatment of reaction time for 2 h in the second step cleanly afforded only **9b**, with no trace of **9′b** (Figure 2). Thus, for the second step of eliminating HCl, controlling the reaction time is especially important.

Next, a variety of aldehydes **3** also reacted with **2** and **7** under the optimized conditions as described above. The reactions of **2**,

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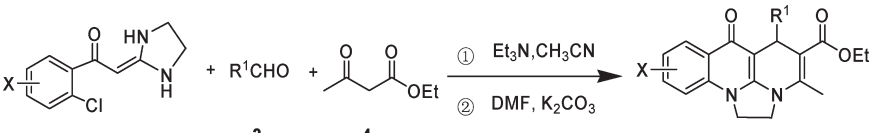
TABLE 1. Synthesis of 6 via a One-Pot Tandem Reaction



2 3 4 6

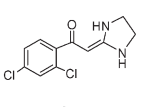
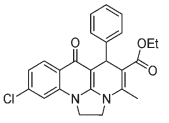
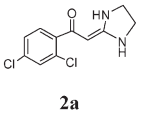
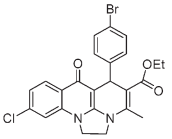
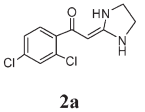
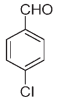
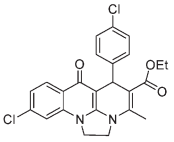
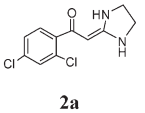
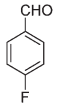
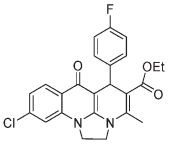
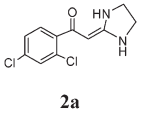
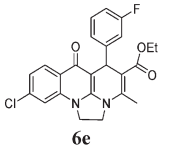
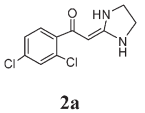
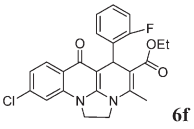
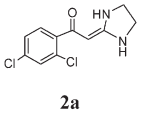
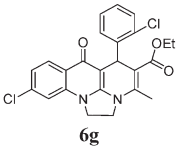
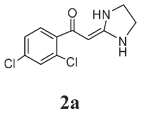
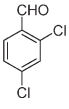
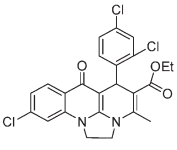
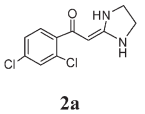
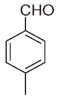
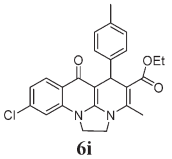
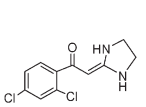
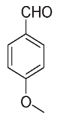
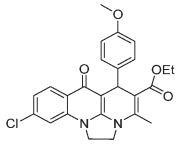
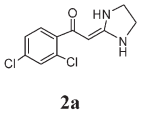
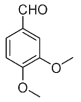
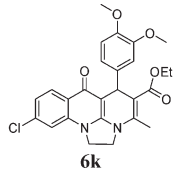
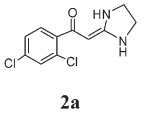
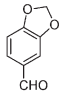
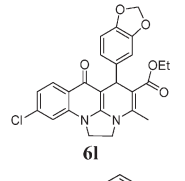
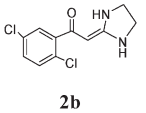
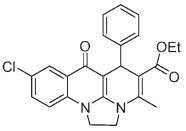
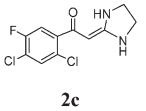
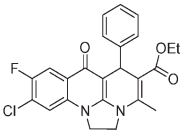
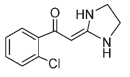
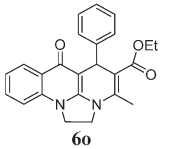
entry	precursor **2**	precursor **3**	product **6**	time (h)[a]	yield (%)[b]
1	 **2a**	 **3a**	 **6a**	8 + 12	87
2	 **2a**	 **3b**	 **6b**	10 + 12	86
3	 **2a**	 **3c**	 **6c**	8 + 12	88
4	 **2a**	 **3d**	 **6d**	8 + 12	93
5	 **2a**	 **3e**	 **6e**	8 + 12	90
6	 **2a**	 **3f**	 **6f**	8 + 12	92
7	 **2a**	 **3g**	 **6g**	8 + 12	87
8	 **2a**	 **3h**	 **6h**	10 + 12	86
9	 **2a**	 **3i**	 **6i**	10 + 12	89

TABLE 1. Continued

entry	precursor **2**	precursor **3**	product **6**	time (h)[a]	yield (%)[b]
10	 **2a**	 **3j**	 **6j**	8 + 12	95
11	 **2a**	 **3k**	 **6k**	11 + 12	86
12	 **2a**	 **3l**	 **6l**	11 + 12	81
13	 **2b**	 **3a**	 **6m**	10 + 12	81
14	 **2c**	 **3a**	 **6n**	5 + 12	92
15	 **2d**	 **3a**	 **6o**	7 + 12	83

[a]The first step time + the second step time. [b]Total isolated yield.

3, and **7**, except 4-nitrobenzaldehyde **3m**, proceeded smoothly with Et_3N (0.4 equiv) in refluxing MeCN followed by stirring the mixture at 81 °C for about 6−8 h, evaporation of the solvent, and then addition of K_2CO_3 in DMF for about 1.5−2 h and led to the formation of tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridines **9** (Table 2).

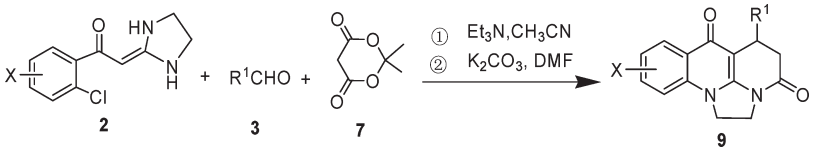
The products **9** have been characterized by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic data, which are in agreement with the proposed structures.

When **3m** was used in this process, workup of the reaction mixture did not afford any expected unaromatized compound **9l**, but only an unexpected compound **9′l**, which is more stable by aerobic oxidation (Scheme 2). In the ^{1}H NMR spectrum of **9′l**, the absence of three protons (δ 2.7−4.6 ppm, CH + CH_2) and existence of olefinic proton (δ 6.03 ppm) indicate that 6π electron system exists in the pyridone moiety (see Supporting Information). From this result, we can deduce that the aldehydes with strong electron-withdrawing groups and prolonging reaction time of the second step would make the hydrogen easier to leave in the air.

On the basis of the above experimental results, a plausible mechanism for the synthesis of tetrahydrobenzo[*b*]imidazo-[3,2,1-*ij*][1,8]naphthyridines **6** or **9** was depicted in Scheme 3. Take Meldrum's acid **7**, for example; first, aldehydes **3** react with **7** through Knoevenagel condensation to give intermediates **A**. Then, the heterocyclic ketene aminals **2**, due to the two strongly electron-withdrawing groups at the α-position of the ketene *N,N*-acetals, acted as heteroene components react with **A** to form the intermediates **B**[24b,c,30] which undergo a rapid imine−enamine tautomerization to give **C**. Next, intramolecular cyclization of **C** with losing a molecule of acetone and decarboxylation of **D** led to the formation of fused heterocyclic imidazo[1,2-*a*]pyridine motifs **8**. Finally, an intramolecular nucleophilic aryl substitution of the *o*-chloro of aryl group (S_NAr) by attack of the NH group leads to new and highly functionalized tetrahydrobenzo[*b*]imidazo-[3,2,1-*ij*][1,8]naphthyridine derivatives **9** with elimination of HCl. The formation of **9′l** occurs through an intramolecular

(30) Zhao, M.-X.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron* **2002**, *58*, 1309–1316.

TABLE 2. Synthesis of 9 via a One-Pot Tandem Reaction



2 **3** **7** **9**

entry	precursor **2**	precursor **3**	product **9**	time (h)[a]	yield (%)[b]
1	**2a**	**3a**	**9a**	8 + 2	85
2	**2a**	**3b**	**9b**	8 + 1.5	82
3	**2a**	**3c**	**9c**	8 + 2	86
4	**2a**	**3d**	**9d**	7 + 2	89
5	**2a**	**3g**	**9e**	8 + 2	87
6	**2a**	**3h**	**9f**	7 + 2	83
7	**2a**	**3i**	**9g**	8 + 2	83
8	**2a**	**3j**	**9h**	8 + 2	80
9	**2b**	**3a**	**9i**	6 + 2	86

[a]The first step time + the second step time. [b]Total isolated yield.

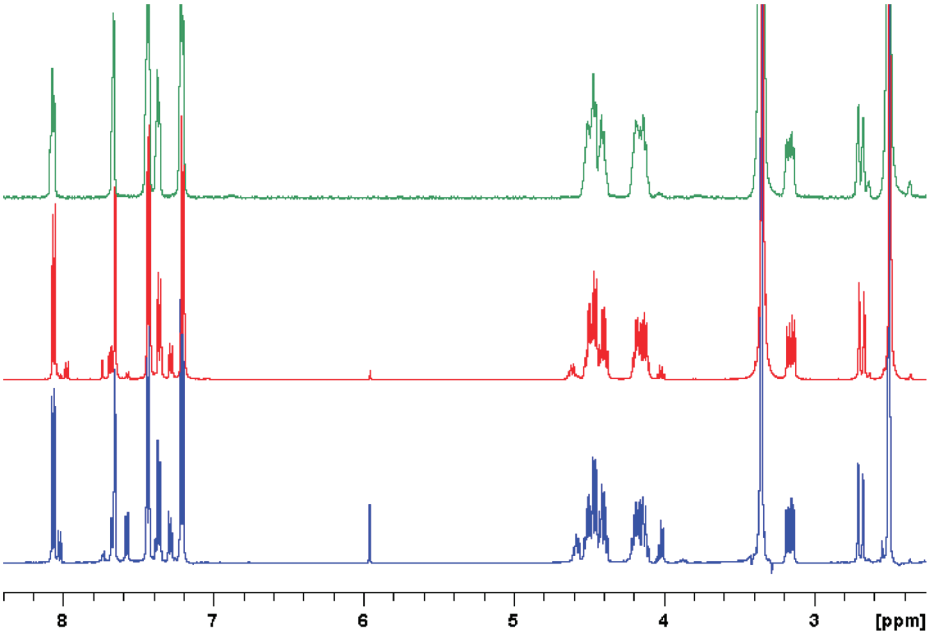


FIGURE 2. Influence of the reaction time for the second step from ^{1}H NMR spectra of **9b**: top, 2 h, **9b**:**9′b** = 1:0.00; middle, 3 h, **9b**:**9′b** = 1:0.02; bottom, 12 h, **9b**:**9′b** = 1:0.17.

nucleophilic aryl substitution of the *o*-chloro of the aryl group (S_NAr) by attack of NH group and quickly undergoing in situ oxidation by air and subsequent dehydrogenation.

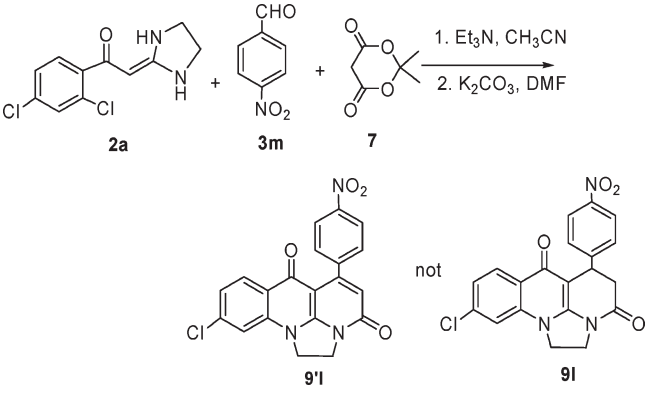
Conclusion

In summary, we have successfully described the application of 2-(2-chloroaroyl)methyleneimidazolidines **2** to synthesize tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridines **6** and **9** in a one-pot, two-step sequential process starting from **2**, arylaldehydes **3**, and ethyl acetoacetate **4** or Meldrum's acid **7**. In these reactions, at least six different active sites are involved; two C−C bonds, two C−N bonds, and two new rings are constructed with all reactants efficiently utilized in the chemical transformation. A possible mechanism including Knoevenagel condensation, aza-ene reaction, intramolecular imine−enamine tautomerization followed by cyclocondensation and intramolecular S_NAr was proposed. Undoubtedly, these domino synthetic strategies open a convenient, effective way to construct the target molecules from readily available starting materials. The wide generation of this process suggests its potential in the synthetic and medicinal importance of this family of compounds and analogues.

Experimental Section

General Procedure for the Preparation of Compounds 6 or 9 (6a, for Example). Et_3N (0.040 g, 0.4 mmol, 0.4 equiv) was added to a solution of 2-(2,4-dichlorobenzoyl)methyleneimidazolidine **2a** (0.257 g, 1.0 mmol), benzaldehyde **3a** (0.127 g, 1.2 mmol), and ethyl acetoacetate **4** (0.156 g, 1.2 mmol) in 10 mL of MeCN. The reaction mixture was refluxed for a certain period of time as indicated by TLC (petroleum ether−EtOAc, 2:1, v/v). The solvent was removed under vacuum, and the residue together with potassium carbonate (1 mmol) was heated to 100 °C in DMF. After completion of the reaction as indicated by TLC (petroleum ether−EtOAc, 2:3, v/v), the mixture was cooled to room temperature, and an amount of ice−water was added to precipitate the products which were then collected by filtration and washed with cool water. The dry solid then was washed with ethanol.

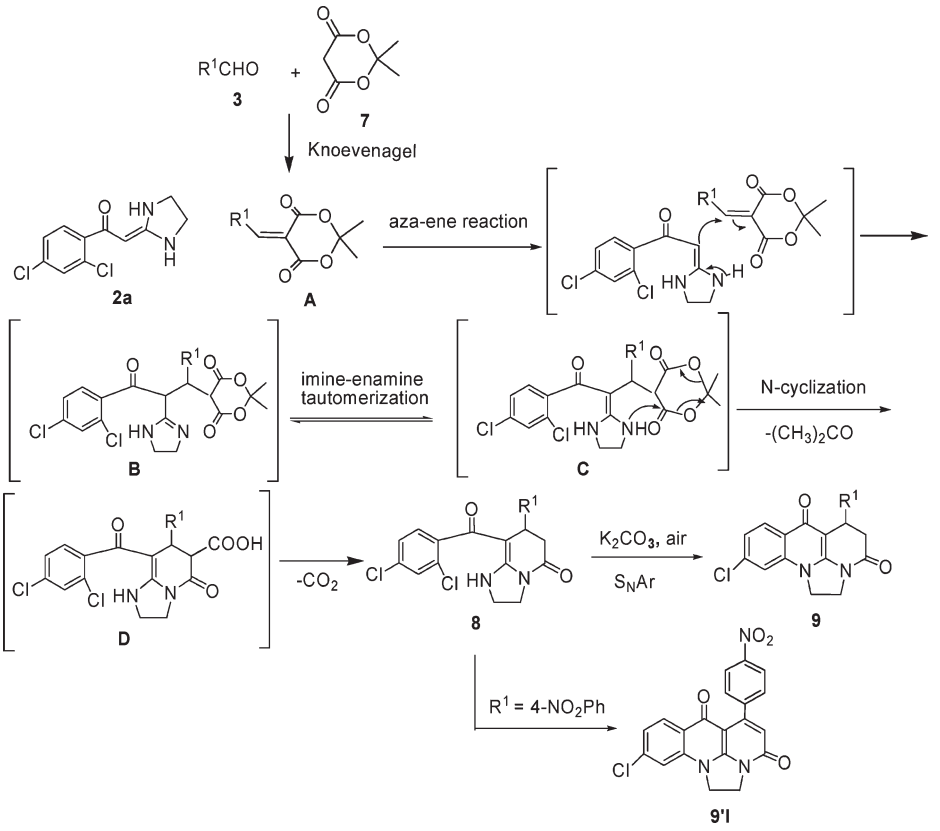
SCHEME 2. Reaction of 2a with 4-Nitrobenzaldehyde and Meldrum's Acid



Ethyl 8-(2,4-dichlorobenzoyl)-5-methyl-7-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate (5a): yellow powder; mp 97−99 °C; IR (KBr, cm^{-1}) 3300, 1691, 1645, 1585, 1554, 1517, 1379, 1225, 838, 769, 705; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.40 (s, 3H, CH_3), 3.86−3.99 (m, 6H, 2 × NCH_2 + OCH_2), 4.56 (s, 1H, CH), 6.36−7.49 (m, 8H, ArH), 9.29 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 14.2 (pyridine-CH_3), 16.4 (OCH_2-CH_3), 40.4 (7-*C*H), 42.8 (NCH_2), 45.1(NCH_2), 59.9 (OCH_2), 89.9 (8-C), 109.2 (6-C), 126.0, 126.7, 127.6, 128.6, 130.0, 134.1, 139.3, 143.0, 147.6 (5-C), 156.5 (9-C), 167.3 (ester C═O), 188.7 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{23}Cl_2N_2O_3$ 457.1086, found 457.1097.

Ethyl 10-chloro-4-methyl-7-oxo-6-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*] [1,8]naphthyridine-5-carboxylate (6a): gray powder; mp 263−265 °C; IR (KBr, cm^{-1}) 1687, 1654, 1613, 1576, 1520, 1388, 1325, 1223, 762, 699; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.98 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.23−4.47 (m, 4H, 2 × NCH_2), 5.17 (s, 1H, CH), 7.05−7.95 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 16.1 (OCH_2CH_3), 38.3 (6-*C*H), 45.4 (NCH_2),

SCHEME 3. Proposed Mechanism for the Reaction (Meldrum's Acid, for Example)



45.5 (NCH_2), 59.8 (OCH_2), 99.1 (6*a*-C), 105.5 (5-C), 115.1, 122.7, 124.0, 126.3, 127.9, 128.2, 128.2, 136.5, 138.1, 146.2, 147.1, 147.4, 167.2 (ester C=O), 173.1 (keto C=O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{22}ClN_2O_3$ 421.1319, found 421.1329.

Ethyl 6-(4-bromophenyl)-10-chloro-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6b): yellow powder; mp 259−260 °C; IR (KBr, cm^{-1}) 1676, 1654, 1613, 1578, 1520, 1385, 1366, 1326, 1221, 828, 778; ^1H NMR (DMSO-d_6) δ 1.10 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, CH_3), 3.99 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.20−4.47 (m, 4H, 2 × NCH_2), 5.11 (s, 1H, CH), 7.22−7.93 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 16.2 (OCH_2CH_3), 38.1 (6-*C*H), 45.4 (NCH_2), 45.5 (NCH_2), 59.9 (OCH_2), 98.6 (6*a*-C), 104.8 (5-C), 115.1, 119.3, 122.8, 123.9, 127.8, 130.5, 131.0, 136.6, 138.0, 146.6, 146.8, 146.9, 167.0 (ester C=O), 173.1 (keto C=O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}BrClN_2O_3$ 499.0424, found 499.0404.

Ethyl 10-chloro-6-(4-chlorophenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6c): yellow powder; mp 266−268 °C; IR (KBr, cm^{-1}) 1676, 1654, 1611, 1575, 1525, 1388, 1369, 1325, 1223, 828, 778; ^1H NMR (DMSO-d_6) δ 1.10 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.23−4.47 (m, 4H, 2 × NCH_2), 5.15 (s, 1H, CH), 7.22−7.95 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 16.2 (OCH_2CH_3), 38.0 (6-*C*H), 45.4 (NCH_2), 45.5 (NCH_2), 59.9 (OCH_2), 98.7 (6*a*-C), 104.8 (5-C), 115.1, 122.8, 123.9, 127.9, 128.1, 130.1, 130.8, 136.6, 138.1, 146.3, 146.7, 147.0, 167.0 (ester C=O), 173.1 (keto C=O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}Cl_2N_2O_3$ 455.0929, found 455.0931.

Ethyl 10-chloro-6-(4-fluorophenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6d): white powder; mp 267−268 °C; IR (KBr, cm^{-1}) 1690, 1654, 1613, 1575, 1520, 1388, 1328, 1221, 833; ^1H NMR (acetone-d_6) δ 1.14 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.62 (s, 3H, CH_3), 4.02 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.45−4.63 (m, 4H, 2 × NCH_2), 5.32 (s, 1H, CH), 6.88−8.06 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.6 (CH_3), 16.2 (OCH_2CH_3), 37.8 (6-*C*H), 45.4 (NCH_2), 45.6 (NCH_2), 59.9 (OCH_2), 99.0 (6*a*-C), 105.3 (5-C), 114.7, 114.9, 115.2, 122.9, 124.0, 128.0, 130.0, 136.6, 138.1, 143.7, 146.5, 147.0, 161.0 (d, ^1J = 240 Hz, F−C couple), 167.2 (ester C=O), 173.2 (keto C=O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}ClFN_2O_3$ 439.1225, found 439.1215.

Ethyl 10-chloro-6-(3-fluorophenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6e): gray powder; mp 256−258 °C; IR (KBr, cm^{-1}) 1685, 1651, 1611, 1583, 1509, 1388, 1366, 1325, 1221, 803, 776; ^1H NMR (DMSO-d_6) δ 1.08 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.48 (s, 3H, CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.22−4.45 (m, 4H, 2 × NCH_2), 5.16 (s, 1H, CH), 6.87−7.94 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.6 (CH_3), 16.2 (OCH_2CH_3), 38.3 (6-*C*H), 45.5 (NCH_2), 45.6 (NCH_2), 59.9 (OCH_2), 98.5 (6*a*-C), 104.7 (5-C), 113.2, 115.0, 115.2, 122.9, 124.0, 124.3, 127.9, 130.0, 136.7, 138.1, 146.9, 150.2, 162.4 (d, ^1J = 241 Hz, F−C couple), 167.1 (ester C=O), 173.2 (keto C=O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}ClFN_2O_3$ 439.1225, found 439.1208.

Ethyl 10-chloro-6-(2-fluorophenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6f): gray powder; mp > 300 °C; IR (KBr, cm^{-1}) 1685, 1657, 1616, 1580, 1520, 1388, 1328, 1226, 872, 759; ^1H NMR (DMSO-d_6) δ 1.09 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, CH_3), 3.94 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.27−4.43 (m, 4H, 2 × NCH_2), 5.34 (s, 1H, CH), 6.97−7.89 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.4 (CH_3), 16.1 (OCH_2CH_3), 32.7 (6-*C*H), 45.4 (2C, NCH_2), 59.8 (OCH_2), 98.4 (6*a*-C), 104.5 (5-C), 115.1, 122.9, 123.9, 124.29, 127.8, 128.3, 131.5, 134.5, 134.6, 136.6, 138.1, 146.4, 147.2, 159.9 (d, ^1J = 245 Hz, F−C couple), 167.1 (ester C=O), 173.0 (keto C=O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}ClFN_2O_3$ 439.1225, found 439.1220.

Ethyl 10-chloro-6-(2-chlorophenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6g): yellow powder; mp 257−258 °C; IR (KBr, cm^{-1}) 1685, 1663, 1616, 1586, 1509, 1388, 1366, 1328, 1221, 1190, 833, 740; ^1H NMR (DMSO-d_6) δ 1.05 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.44 (s, 3H, CH_3), 3.93 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.25−4.41 (m, 4H, 2 × NCH_2), 5.40 (s, 1H, CH), 7.05−7.85 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.4 (CH_3), 16.1 (OCH_2CH_3), 36.9 (6-*C*H), 45.3 (2C, NCH_2), 59.7 (OCH_2), 98.6 (6*a*-C), 104.9 (5-C), 115.0, 122.8, 123.9, 127.1, 127.8, 127.9, 129.3, 132.2, 132.9, 136.6, 138.1, 144.7, 145.8, 147.2, 167.1 (ester C═O), 173.0 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}Cl_2N_2O_3$ 455.0929, found 455.0946.

Ethyl 10-chloro-6-(2,4-dichlorophenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6h): gray powder; mp 258−260 °C; IR (KBr, cm^{-1}) 1678, 1654, 1611, 1578, 1515, 1221, 828, 778; ^1H NMR (acetone-d_6) δ 1.14 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.57 (s, 3H, CH_3), 4.05 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.46−4.59 (m, 4H, 2 × NCH_2), 5.54 (s, 1H, CH), 7.12−7.97 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.6 (CH_3), 16.2 (OCH_2CH_3), 36.7 (6-*C*H), 45.4 (2C, NCH_2), 59.9 (OCH_2), 98.4 (6*a*-C), 104.4 (5-C), 115.2, 123.0, 123.9, 127.3, 128.6, 131.4, 133.5, 134.0, 136.7, 138.2, 144.0, 146.4, 147.1, 167.0 (ester C═O), 173.0 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{20}Cl_3N_2O_3$ 489.0540, found 489.0525.

Ethyl 10-chloro-4-methyl-7-oxo-6-(*p*-tolyl)-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6i): yellow powder; mp 270−272 °C; IR (KBr, cm^{-1}) 1696, 1654, 1613, 1578, 1520, 1388, 1369, 1325, 1221, 1199, 839, 789; ^1H NMR (DMSO-d_6) δ 1.13 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.18 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.98 (t, J = 7 Hz, 2H, OCH_2CH_3), 4.21−4.44 (m, 4H, 2 × NCH_2), 5.12 (s, 1H, CH), 6.96−7.94 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.6 (CH_3), 16.1 (OCH_2CH_3), 21.1 (Ar-CH_3), 37.9 (6-*C*H), 45.4 (NCH_2), 45.6 (NCH_2), 59.8 (OCH_2), 99.3 (6*a*-C), 105.7 (5-C), 115.1, 122.8, 124.1, 128.0, 128.1, 128.8, 135.3, 136.5, 138.1, 144.6, 146.0, 147.1, 167.3 (ester C═O), 173.1 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{25}H_{24}ClN_2O_3$ 435.1475, found 435.1497.

Ethyl 10-chloro-6-(4-methoxyphenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6j): yellow powder; mp 264−266 °C; IR (KBr, cm^{-1}) 1701, 1654, 1613, 1575, 1525, 1388, 1366, 1328, 1251, 842, 789, 754; ^1H NMR (DMSO-d_6) δ 1.13 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.98 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.19−4.45 (m, 4H, 2 × NCH_2), 5.10 (s, 1H, CH), 6.72−7.94 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.6 (CH_3), 16.1 (OCH_2CH_3), 37.4 (6-*C*H), 45.3 (NCH_2), 45.5 (NCH_2), 55.4 (OCH_3), 59.8 (OCH_2), 99.4 (6*a*-C), 105.8 (5-C), 113.5, 115.0, 122.7, 123.99, 127.9, 129.1, 136.5, 138.0, 139.7, 145.7, 147.0, 157.9, 167.3 (ester C═O), 173.1 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{25}H_{24}ClN_2O_4$ 451.1425, found 451.1425.

Ethyl 10-chloro-6-(3,4-dimethoxyphenyl)-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6k): yellow powder; mp 237−239 °C; IR (KBr, cm^{-1}) 1685, 1660, 1613, 1575, 1520, 1388, 1328, 1265, 1226, 806; ^1H NMR (DMSO-d_6) δ: 1.15 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.50 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.02(q, J = 7 Hz, 2H, OCH_2CH_3), 4.23−4.48 (m, 4H, 2 × NCH_2), 5.14 (s, 1H, CH), 6.96−7.98 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.7 (CH_3), 16.1 (OCH_2CH_3), 37.7 (6-*C*H), 45.4 (NCH_2), 45.6 (NCH_2), 56.0 (2C, OCH_3), 59.8 (OCH_2), 99.4 (6*a*-C), 105.7 (5-C), 112.2, 112.8, 115.1, 120.0, 122.8, 124.1, 128.0, 136.5, 138.1, 140.3, 145.8, 147.1, 147.7, 148.4, 167.4 (ester C═O), 173.3 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{26}H_{26}ClN_2O_5$ 481.1530, found 481.1521.

Ethyl 6-(benzo[*d*][1,3]dioxol-5-yl)-10-chloro-4-methyl-7-oxo-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6l): yellow powder; mp 257−259 °C; IR (KBr, cm^{-1}) 1698, 1659, 1616, 1576, 1522, 1339, 1231, 795, 673; ^1H NMR (DMSO-d_6) δ 1.12 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.50 (s, 3H, CH_3), 4.00 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.23−4.47 (m, 4H, 2 × NCH_2), 5.10 (s, 1H, CH), 5.88 (s, 2H, OCH_2O), 6.69−7.96 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.7 (CH_3), 16.2 (OCH_2CH_3), 38.0 (6-*C*H), 45.4 (NCH_2), 45.6 (NCH_2), 59.9 (OCH_2), 99.2 (6*a*-C), 101.1 (OCH_2O), 105.6 (5-C), 108.0, 108.9, 115.1, 121.1, 122.8, 124.0, 128.0, 136.6, 138.1, 141.6, 145.8, 146.0, 147.1, 147.2, 167.3 (ester C═O), 173.2 (keto C═O), HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{25}H_{22}ClN_2O_5$ 465.1217, found 465.1195.

Ethyl 9-chloro-4-methyl-7-oxo-6-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6m): gray powder; mp 251−253 °C; IR (KBr, cm^{-1}) 1695, 1659, 1616, 1576, 1540, 1518, 1328, 806, 702; ^1H NMR (DMSO-d_6) δ 1.11 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.98(q, J = 7 Hz, 2H, OCH_2CH_3), 4.24−4.48 (m, 4H, 2 × NCH_2), 5.19 (s, 1H, CH), 7.06−7.89 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 16.1 (OCH_2CH_3), 38.3 (6-*C*H), 45.4 (NCH_2), 45.6 (NCH_2), 59.8 (OCH_2), 99.2 (6*a*-C), 105.4 (5-C), 117.8, 125.0, 126.3, 126.5, 127.3, 128.2, 131.6, 135.9, 146.3, 147.1, 147.3, 167.2 (ester C═O), 172.4 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{22}ClN_2O_3$ 421.1319, found 421.1335.

Ethyl 10-chloro-9-fluoro-4-methyl-7-oxo-6-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6n): gray powder; mp 249−251 °C; IR (KBr, cm^{-1}) 1687, 1652, 1587, 1522, 1428, 1389, 1328, 1241, 1213, 1108, 975, 835, 698; ^1H NMR (DMSO-d_6) δ 1.09 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.24−4.49 (m, 4H, 2 × NCH_2), 5.16 (s, 1H, CH), 7.05−7.78 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 16.1 (OCH_2CH_3), 38.4 (6-*C*H), 45.6 (NCH_2), 45.8 (NCH_2), 59.9 (OCH_2), 99.9 (6*a*-C), 105.6 (5-C), 112.2, 112.4, 117.8, 123.9, 124.1, 125.3, 126.4, 128.2, 128.3, 134.2, 146.1, 147.2, 147.3, 153.4 (d, ^1J = 242 Hz, F−C couple), 167.2 (ester C═O), 172.3 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{21}ClFN_2O_3$ 439.1225, found 439.1231.

Ethyl 4-methyl-7-oxo-6-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylate (6o): gray powder; mp 238−240 °C; IR (KBr, cm^{-1}) 1691, 1655, 1616, 1580, 1540, 1522, 1328, 759; ^1H NMR (DMSO-d_6) δ 1.11 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.98 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.26−4.47 (m, 4H, 2 × NCH_2), 5.21 (s, 1H, CH), 7.05−7.98 (m, 9H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.7 (CH_3), 16.2 (OCH_2CH_3), 38.3 (6-*C*H), 45.2 (NCH_2), 45.6 (NCH_2), 59.8 (OCH_2), 98.8 (6*a*-C), 105.3 (5-C), 115.4, 122.6, 125.4, 126.0, 126.3, 128.2, 131.9, 137.2, 146.6, 146.9, 147.7, 167.4 (ester C═O), 173.8 (keto C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{24}H_{23}N_2O_3$ 387.1709, found 387.1700.

8-(2,4-Dichlorobenzoyl)-7-phenyl-2,3,6,7-tetrahydroimidazo-[1,2-*a*]pyridine-5-(1*H*)-one (8a): yellow powder; mp 212−214 °C; IR (KBr, cm^{-1}) 3284, 1687, 1639, 1583, 1535, 1370, 1321, 843, 729, 703; ^1H NMR ($CDCl_3$) δ: 2.74 (dd, J = 1.5 Hz, 16.5 Hz, 1H, C(O)-CH_2), 3.02 (dd, J = 7.5 Hz, 16.5 Hz, 1H, C(O)CH_2), 3.74−4.16 (m, 5H, 2 × NCH_2 + CH), 6.63−7.34 (m, 8H, ArH), 9.56 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 37.9 (7-*C*H), 40.4 (6-CH_2), 41.9 (NCH_2), 42.8 (NCH_2), 88.9 (8-C), 126.4, 126.7, 126.80, 128.6, 129.2, 134.5, 138.6, 143.6, 157.1, 167.7 (5-C═O), 188.4 (C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{17}Cl_2N_2O_2$ 387.0667, found 387.0656.

10-Chloro-6-phenyl-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*]-[1,8]naphthyidine-4,7-dione (9a): yellow powder; mp 252−254 °C; IR (KBr, cm^{-1}) 1701, 1685, 1652, 1580, 1506, 1366, 1229, 833, 737, 699; ^1H NMR (DMSO-d_6) δ 2.68 (d, J = 16.5 Hz, 1H, C(O)CH_2), 3.16 (dd, J = 8 Hz, 16 Hz, 1H, C(O)CH_2), 4.13−4.51 (m, 5H, 2 × NCH_2 + CH), 7.18−8.08 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6) δ 34.5 (6-*C*H), 42.9 (NCH_2), 45.8 (NCH_2), 99.8 (6*a*-C), 115.7, 123.6, 124.0, 127.1, 128.3, 129.0, 136.8, 138.3, 144.0, 148.4, 168.0 (4-C═O), 173.3 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{16}ClN_2O_2$ 351.0900, found 351.0914.

6-(4-Bromophenyl)-10-chloro-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9b): yellow powder; mp

239−241 °C; IR (KBr, cm^{-1}) 1687, 1646, 1616, 1583, 1517, 1369, 1229, 839, 781; ^1H NMR (DMSO-d_6) δ 2.71 (d, J = 17 Hz, 1H, C(O)CH_2), 3.17 (dd, J = 8 Hz, 16.5 Hz, 1H, C(O)CH_2), 4.12−4.51 (m, 5H, 2 × NCH_2 + CH), 7.20−8.07 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 34.1 (6-*C*H), 39.2 (5-*C*H_2), 43.0 (NCH_2), 46.0 (NCH_2), 99.3 (6*a*-C), 115.8, 123.7, 124.0, 128.3, 129.2, 129.5, 130.8, 137.0, 138.4, 143.5, 148.6, 167.9 (4-C═O), 173.3 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{15}BrClN_2O_2$ 429.0005, found 429.0024.

10-Chloro-6-(4-chlorophenyl)-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9c): yellow powder; mp 223−225 °C; IR (KBr, cm^{-1}) 1701, 1687, 1638, 1616, 1578, 1520, 1369, 1229, 839, 784; ^1H NMR (DMSO-d_6) δ 2.67 (d, J = 16.5 Hz, 1H, C(O)CH_2), 3.16 (dd, J = 9.5 Hz, 17 Hz, 1H, C(O)CH_2), 4.12−4.51 (m, 5H, 2 × NCH_2 + CH), 7.26−8.07 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 34.1 (6-*C*H), 39.2 (5-*C*H_2), 43.0 (N*C*H_2), 46.0 (N*C*H_2), 99.4 (6*a*-C), 115.8, 123.7, 124.0, 128.3, 128.9, 129.1, 131.7, 137.0, 138.3, 143.0, 148.6, 167.9 (4-C═O), 173.3 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{15}Cl_2N_2O_2$ 385.0511, found 385.0514.

10-Chloro-6-(4-fluorophenyl)-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9d): yellow powder; mp 169−171 °C; IR (KBr, cm^{-1}) 1707, 1638, 1611, 1569, 1534, 1366, 1232, 842, 781, 691; ^1H NMR (DMSO-d_6) δ 2.67 (d, J = 16.5 Hz, 1H, C(O)CH_2), 3.15 (dd, J = 8 Hz, 17 Hz, 1H, C(O)CH_2), 4.12−4.50 (m, 5H, 2 × NCH_2 + CH), 7.04−8.07 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 33.9 (6-*C*H), 43.0 (N*C*H_2), 45.9 (N*C*H_2), 99.8 (6*a*-*C*), 115.6, 115.7, 123.6, 124.0, 128.3, 129.0, 129.1, 136.9, 138.3, 140.2, 148.5, 161.5 (d, ^1J = 241 Hz, F−C couple), 168.0 (4-C═O), 173.3 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{15}ClFN_2O_2$ 369.0806, found 369.0789.

10-Chloro-6-(2-chlorophenyl)-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9e): yellow powder; mp 242−244 °C; IR (KBr, cm^{-1}) 1705, 1648, 1616, 1587, 1540, 1472, 1371, 1277, 961, 784, 748, 677; ^1H NMR (DMSO-d_6) δ 2.52 (dd, J = 8 Hz, 15.5 Hz, 1H, C(O)CH_2), 3.24 (dd, J = 9 Hz, 17 Hz, 1H, C(O)CH_2), 4.16−4.80 (m, 5H, 2 × NCH_2 + CH), 7.04−8.02 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ: 32.2 (6-*C*H), 38.6 (5-*C*H_2), 43.0 (N*C*H_2), 46.1 (N*C*H_2), 97.9 (6*a*-C), 115.9, 123.7, 124.0, 128.0, 128.2, 129.1, 130.3, 133.0, 137.1, 138.6, 140.5, 149.5, 167.2 (4-C═O), 173.2 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{15}Cl_2N_2O_2$ 385.0511, found 385.0510.

10-Chloro-6-(2,4-dichlorophenyl)-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9f): yellow powder; mp 182−184 °C; IR (KBr, cm^{-1}) 1697, 1648, 1617, 1584, 1541, 1521, 1472, 1373, 1093, 817, 785; ^1H NMR (DMSO-d_6) δ 2.54 (1H, C(O)CH_2), 3.26 (dd, J = 9 Hz, 16.5 Hz, 1H, C(O)CH_2), 4.15−4.76 (m, 5H, 2 × NCH_2 + CH), 7.10−8.04 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6) δ 31.9 (6-*C*H), 38.2 (5-*C*H_2), 43.0 (N*C*H_2), 46.0 (N*C*H_2), 97.4 (6*a*-C), 115.8, 123.7, 123.8, 127.9, 128.1, 129.6, 129.7, 132.6, 133.9, 137.0, 138.5, 139.7, 149.4, 166.8 (4-C═O), 173.1 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{14}N_2O_2Cl_3$ 419.0121, found 419.0134.

10-Chloro-6-(*p*-tolyl)-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9g): yellow powder; mp 196−198 °C; IR (KBr, cm^{-1}) 1692, 1648, 1617, 1584, 1540, 1519, 1372, 1229, 824, 783; ^1H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 2.65 (d, J = 16.5 Hz, 1H, C(O)CH_2), 3.11 (dd, J = 8 Hz, 16.5 Hz, 1H, C(O)CH_2), 4.11−4.52 (m, 5H, 2 × NCH_2 + CH), 7.03−8.07 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 21.0 (Ar-*C*H_3), 34.1 (6-*C*H), 42.9 (N*C*H_2), 45.8 (N*C*H_2), 100.0 (6*a*-C), 115.7, 123.5, 124.0, 126.9, 128.3, 129.5, 136.1, 136.8, 138.3, 141.0, 148.4, 168.1 (4-C═O), 173.3 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{21}H_{18}ClN_2O_2$ 365.1057, found 365.1051.

10-Chloro-6-(4-methoxyphenyl)-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9h): yellow powder; mp 224−226 °C; IR (KBr, cm^{-1}) 1702, 1685, 1651, 1615, 1588, 1540, 1514, 1373, 1248, 839, 782; ^1H NMR (DMSO-d_6) δ 2.66 (d, J = 16 Hz, 1H, C(O)CH_2), 3.11 (dd, J = 8 Hz, 17 Hz, 1H, C(O)CH_2), 3.68 (s, 3H, OCH_3), 4.12−4.54 (m, 5H, 2 × NCH_2 + CH), 6.79−8.08 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 33.7 (6-*C*H), 42.9 (N*C*H_2), 45.8 (N*C*H_2), 55.5 (O*C*H_3), 100.2 (6*a*-C), 114.3, 123.5, 124.0, 128.1, 135.9, 136.8, 138.3, 148.3, 158.4, 168.2 (4-C═O), 173.3 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{21}H_{18}ClN_2O_3$ 381.1006, found 381.1011.

9-Chloro-6-phenyl-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9i): yellow powder; mp > 300 °C; IR (KBr, cm^{-1}) 1691, 1641, 1616, 1587, 1547, 1515, 1418, 1382, 1321, 1231, 1166, 907, 705; ^1H NMR (DMSO-d_6) δ 2.70 (d, J = 16.5 Hz, 1H, C(O)CH_2), 3.15 (dd, J = 7.5 Hz, 17 Hz, 1H, C(O)CH_2), 4.17−4.53 (m, 5H, 2 × NCH_2 + CH), 7.18−8.01 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6) δ 34.6 (6-*C*H), 42.9 (N*C*H_2), 45.9 (N*C*H_2), 99.8 (6*a*-C), 118.5, 125.3, 126.5, 127.1, 128.1, 129.0, 132.0, 136.1, 144.0, 148.5, 168.1 (4-C═O), 172.7 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{16}ClN_2O_2$ 351.0900, found 351.0887.

10-Chloro-9-fluoro-6-phenyl-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9j): yellow powder; mp 240−242 °C; IR (KBr, cm^{-1}) 1691, 1644, 1594, 1547, 1518, 1421, 1378, 1238, 1015, 950, 795, 768, 698; ^1H NMR (DMSO-d_6) δ 2.70 (d, J = 15.5 Hz, 1H, C(O)CH_2), 3.16 (dd, J = 8 Hz, 16.5 Hz, 1H, C(O)CH_2), 4.14−4.54 (m, 5H, 2 × NCH_2 + CH), 7.17−7.91 (m, 7H, ArH); ^{13}C NMR (DMSO-d_6) δ 34.1 (6-*C*H), 42.4 (N*C*H_2), 45.7 (N*C*H_2), 99.0 (6*a*-C), 112.0, 112.2, 118.1, 123.8, 124.0, 124.9, 126.6, 128.5, 133.9, 143.4, 148.2, 153.3 (d, ^1J = 242 Hz, F−C couple), 167.6 (4-C═O), 172.0 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{15}ClFN_2O_2$ 369.0806, found 369.0809.

6-Phenyl-1,2,5,6-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9k): yellow powder; mp 254−256 °C; IR (KBr, cm^{-1}) 1698, 1637, 1616, 1576, 1540, 1522, 1468, 1446, 1310, 1159, 766, 738, 709; ^1H NMR (DMSO-d_6) δ 2.70 (d, J = 16.5 Hz, 1H, C(O)CH_2), 3.15 (dd, J = 8 Hz, 17 Hz, 1H, C(O)CH_2), 4.11−4.53 (m, 5H, 2 × NCH_2 + CH), 7.14−8.10 (m, 9H, ArH); ^{13}C NMR (DMSO-d_6) δ 34.6 (6-*C*H), 42.8 (N*C*H_2), 45.6 (N*C*H_2), 99.3 (6*a*-C), 116.0, 123.3, 125.4, 126.2, 127.0, 127.1, 128.9, 132.1, 137.4, 144.2, 148.0, 168.1 (4-C═O), 173.9 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{17}N_2O_2$ 317.1290, found 317.1282.

10-Chloro-6-(4-nitrophenyl)-1,2-dihydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-4,7-dione (9′l): yellow powder; mp 279−281 °C; IR (KBr, cm^{-1}) 1665, 1635, 1594, 1564, 1536, 1509, 1347, 1292, 935, 836, 784; ^1H NMR (DMSO-d_6) δ 4.45 (t, J = 9.5 Hz, 2H, NCH_2), 4.61 (t, J = 9.5 Hz, 2H, NCH_2), 6.03 (s, 1H, =CH), 7.37−8.24 (m, 7H, ArH); ^{13}C NMR (TFA-*d*) δ 46.5 (N*C*H_2), 49.5 (N*C*H_2), 102.7 (6*a*-C), 120.3, 126.1, 129.8, 130.3, 131.3, 139.7, 145.0, 147.8, 150.6, 151.5, 153.8, 172.9 (7-C═O); HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{20}H_{13}ClN_3O_4$ 394.0595, found 394.0595.

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Supporting Information Available: Experimental procedures, copies of ^1H NMR, ^{13}C NMR, and HRMS spectra of all new compounds, and X-ray data for compound **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.