JOC The Journal of Organic Chemistry

Article

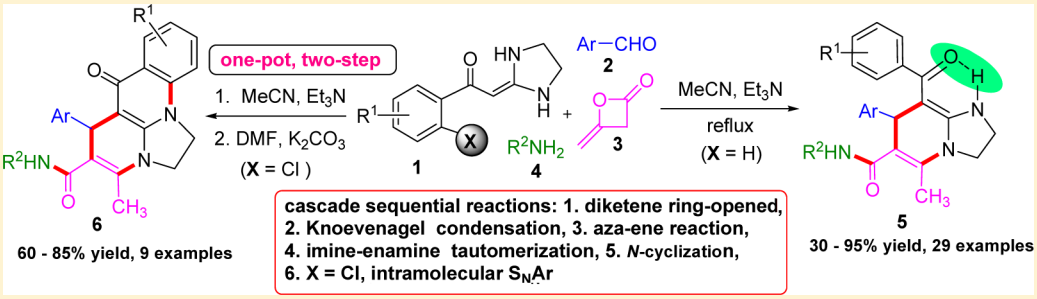
pubs.acs.org/joc

Four-Component Cascade Heteroannulation of Heterocyclic Ketene Aminals: Synthesis of Functionalized Tetrahydroimidazo[1,2-*a*]pyridine Derivatives

Ming Li,* Peng Shao, Shu-Wen Wang, Wei Kong, and Li-Rong Wen*

State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, People's Republic of China

Supporting Information



ABSTRACT: An efficient and straightforward four-component synthetic protocol has been developed to synthesize imidazo[1,2-*a*]pyridines and imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives incorporating medicinally privileged heterosystems from heterocyclic ketene aminals, aldehydes, diketene, and amines via cascade reactions, including diketene ring-opening, Knoevenagel condensation, aza−ene reaction, imine−enamine tautomerization, cyclocondensation, and intramolecular S_NAr. This strategy can provide an alternative approach for easy access to the highly substituted imidazo[1,2-*a*]pyridine derivatives in moderate to good yields using four simple and readily available building blocks under mild conditions. Importantly, the unusual splitting peaks in the ^1H NMR spectra of the products derived from heterocyclic ketene aminals with an *o*-halogen atom on the aryl ring were explained reasonably by varying the temperature in NMR analysis.

INTRODUCTION

The imidazo[1,2-*a*]pyridine nucleus is an important privileged heterocyclic scaffold in numerous biologically active pharmacophores. For example, there this scaffold exists in prominent anxiolytic drugs such as alpidem (**I**)[1] and necopidem (**II**),[2] PI3KR inhibitors (**III**),[3] inhibitors of TNF-α expression in T cells (**IV**),[4] allosteric modulators of the metabotropic glutamate 2 (mGlu2) receptor (**V**),[5] and insecticide against pea aphids (**VI**) (Figure 1).[6] In addition, the imidazo[1,2-*a*]pyridines show antibacterial,[7] anti-inflammatory and analgesic,[8] and hypnoselective and anxioselective[9] activities. Although a variety of methodologies and protocols have been reported by a number of organic or pharmaceutical chemists,[10] the preparation of some specific substituted patterns remains difficult. It is of great importance to explore a novel and efficient synthetic method to meet increasing scientific and practical demands.

Carbon−carbon and carbon−heteroatom bond-forming reactions are central to organic synthesis. The rich and fascinating chemistry that stems from multicomponent reactions (MCRs) provides a robust approach for the synthesis of diverse and complex "druglike" heterocyclic compounds.[11] MCRs are important for generating high levels of diversity, giving rise to complex structures by simultaneous formation of two or more bonds from simple substrates.[12] The design of a multicomponent cascade reaction from simple and readily available materials to generate complex molecular architectures is significant and attractive, especially for the synthesis of privileged heterocyclic scaffolds.[13]

Heterocyclic ketene aminals (HKAs),[14] which show structural features with general formulas **A** and **B** (Figure 2), have proven to be important synthons in organic synthesis. Reactions of cyclic ketene aminals with a variety of biselectrophilic groups have so far been applied to construct five- and six-membered and fused heterocycles during the past few years.[15] Meanwhile, diketene as a strained molecule, which is readily ring-opened to react with an amine in situ at room temperature, has been explored as a versatile synthetic building block for the construction of *N*-heterocyclic compounds in a number of new diketene-based reactions.[16]

In continuation of our research interests regarding the development of the synthetic utility of HKAs[17] and on the basis of our previous endeavors in exploring novel and practical MCRs to synthesize useful heterocyclic compounds,[18] we report herein a simple and convenient protocol by extensive use of aza−ene reaction for synthesis of imidazo[1,2-*a*]pyridine

Received: July 2, 2012
Published: September 12, 2012

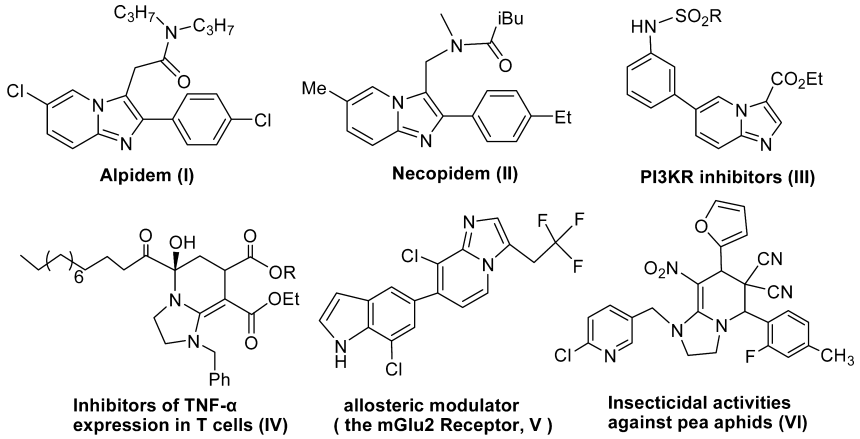


Figure 1. Selected examples of imidazo[1,2-*a*]pyridines with biological and medicinal activities.

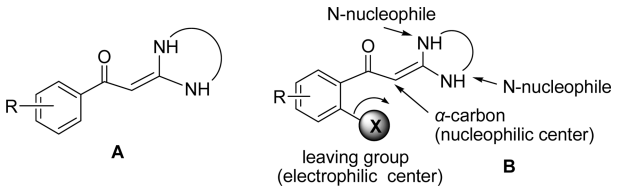
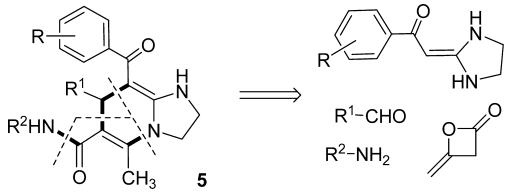


Figure 2. Functionalized heterocyclic ketene aminals.

derivatives via a four-component reaction involving the assembly of the scaffold from [3 + 2 + 1] atom fragments (Scheme 1). In this four-component domino process, at least

Scheme 1. Retrosynthesis Analysis of Imidazo[1,2-*a*]pyridines



nine chemically distinct reactive sites participated in the chemical transformation that led to the concomitant creation of four new bonds (two C−C bonds and two C−N bonds) and one new ring was generated. So far, to the best of our knowledge, this is the first protocol for the four-component reaction (4CR) for the synthetic application of HKAs to synthesize novel imidazo[1,2-*a*]pyridine and imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives.

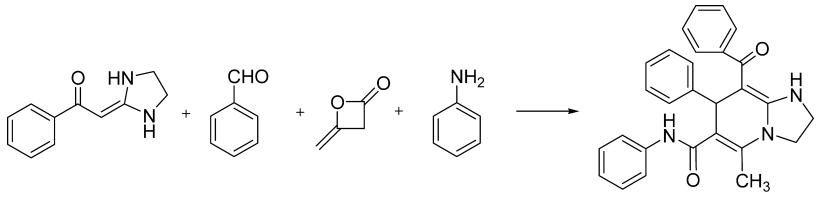
RESULTS AND DISCUSSION

In the initial experiment, we explored the optimum conditions for the four-component reaction to synthesize 8-benzoyl-5-methyl-*N*,7-diphenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (**5a**) by using 2-(imidazolidin-2-ylidene)-1-phenylethanone (**1a**), benzaldehyde (**2a**), diketene (**3**), and phenylamine (**4a**) as model substrates. The effects of different catalysts, solvents, and temperatures on the yields of the model reaction were examined (Table 1). Obviously, without any catalyst, the reaction did not take place at room temperature, even in refluxing acetonitrile (Table 1, entries 1 and 2). When Et_3N (0.5 equiv) was added, the reaction proceeded smoothly in refluxing MeCN to give the corresponding product **5a** in a yield of 73% (Table 1, entry 3). Then other organic bases such as DBU, DABCO, DMAP, and piperidine and inorganic bases such as K_2CO_3 and KOH were employed as the catalyst to improve the yield of **5a**. However, compared to Et_3N, they gave relatively lower yields (Table 1, entries 4−9). Next the amount of Et_3N was investigated, and the results showed that increasing or decreasing the amount of Et_3N resulted in slightly lower yields (Table 1, entries 10 and 11). The utility of other solvents, such as CH_3OH, EtOH, CH_2Cl_2, and DMF, was unsatisfactory (Table 1, entries 12−15). The solvent-free condition was also attempted to improve the yield. However, with no catalyst or with Et_3N as the catalyst, the reactions did not give satisfactory yields (Table 1, entries 16 and 17). Therefore, it could be concluded that the best reaction conditions for the preparation of **5a** were 0.5 equiv of Et_3N as the catalyst in refluxing MeCN (bold in the table).

To further demonstrate the scope and versatility of this procedure for the synthesis of tetrahydroimidazo[1,2-*a*]-pyridines **5**, seven HKAs (**1a−g**), ten aromatic aldehydes (**2a−j**), and seven amines (**4a−g**) were employed to react with **3** under the optimized conditions (Table 2). As can be seen from Table 2, all reactions proceeded well and gave rise to the corresponding products **5** as a racemic mixture. For precursors **1**, the larger the number of electron-withdrawing groups on the aryl ring, the higher the yields of products **5** (Table 2, entries 20 and 21). For precursors **2**, the aldehydes with an electron-withdrawing group on the aryl ring gave higher yields than those with an electron-donating group (Table 2, entries 23−27). For both precursors **1** and **2**, however, the positions of substituents on the aryl ring had almost no effect on the yields of products **5**, except a large group at the *ortho* position in aromatic aldehydes due to steric hindrance (Table 2, entry 8). For precursors **4**, both the aliphatic amines and the aromatic amines with a *para*-electron-donor group such as a methyl group as well as aniline could afford good yields (Table 2, entries 3, 11, 12, and 16), while the aromatic amines with a *para*-electron-withdrawing group such as a bromo group only gave moderate yields (Table 2, entry 14). However, interestingly, the aromatic amines with an *ortho*-electron-donor group such as a methyl group or an *ortho*-electron-withdrawing group such as a bromo group could decrease the reactivity, which should be subject to steric hindrance (Table 2, entries 13 and 15). Unfortunately, we did not obtain the expected products when aliphatic aldehydes such as *n*-butyraldehyde, heteroaromatic aldehydes such as furan-2-

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

Table 1. Optimization of Reaction Conditions for the Synthesis of 5a[a]



1a 2a 3 4a 5a

entry	catalyst (concn/mmol %)	solvent	temp/°C	yield[b]/%
1		CH_3CN	rt	NR
2		CH_3CN	reflux	NR
3	**Et_3N (0.5)**	**CH_3CN**	**reflux**	**73**
4	DBU (0.5)	CH_3CN	reflux	38
5	DABCO (0.5)	CH_3CN	reflux	41
6	DMAP (0.5)	CH_3CN	reflux	36
7	piperidine (0.5)	CH_3CN	reflux	39
8	K_2CO_3 (0.5)	CH_3CN	reflux	35
9	KOH (0.5)	CH_3CN	reflux	32
10	Et_3N (0.3)	CH_3CN	reflux	65
11	Et_3N (0.7)	CH_3CN	reflux	70
12	Et_3N (0.5)	CH_3OH	reflux	30
13	Et_3N (0.5)	EtOH	reflux	39
14	Et_3N (0.5)	CH_2Cl_2	reflux	27
15	Et_3N (0.5)	DMF	100	36
16			70	20[c]
17	Et_3N (0.5)		70	42[c]

[a]Reactions were carried out using **1a** (1.0 mmol), **2a** (1.0 mmol), **3** (1.0 mmol), **4a** (1.0 mmol), base, and solvent (5 mL) for 18 h. [b]Isolated yield. [c]Reaction time 3 h.

carbaldehyde, and long-chain aliphatic amines such as laurylamine were used, which can be ascribed to self-condensation of aliphatic aldehydes and low activity of the heteroaromatic aldehydes and long-chain aliphatic amines under these reaction conditions.

The structures of the products **5** were identified by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data and unequivocally confirmed by X-ray diffraction analysis of a monocrystal of **5cc** (Figure S2 in the Supporting Information). It is worth mentioning that, in the ^{1}H NMR spectra of compounds **5s**−**5cc** with a chlorine atom at the *ortho* position on the aromatic ring from heterocyclic ketene aminals **1** (Table 2, entries 19−29), there exist three sets of unusual splitting peaks. Take the compound **5cc**, for example (Figure S2, bottom, in the Supporting Information). For the signal of the chiral *CH (δ 4.5), an expected singlet appeared as a doublet. The same phenomenon could also be observed at δ 6.4, which was the signal of the aryl group with an *o*-chlorine group, and at δ 9.6, which was attributed to the NH of the imidazole ring. For compounds **5a**−**r** without an *o*-chlorine atom on the aryl ring, however, this phenomenon did not occur. Therefore, it is necessary to identify the factors that lead to this phenomenon. From the crystallographic data of compound **5cc**, a strong intramolecular O(1)···H−N(1) hydrogen bond was observed, which restricted the free rotation of the carbonyl group. We reasoned that this result could lead to two isomers due to the steric hindrance of the *o*-chlorine atom (Figure 3).

To verify this inference, we examined the ^{1}H NMR spectrum of compound **5cc** in DMSO-d_6 at a higher temperature of 60 °C (Figure S2, top, in the Supporting Information). As expected, in the ^{1}H NMR spectra of **5cc** at 60 °C, the three original sets of splitting peaks disappeared and were replaced by three single peaks due to these hydrogen atoms in individual average environments resulting from rapid rotation of the aryl ring at high temperature. It was testified fully that the splitting peaks arose from the rotational barrier contributed by the *o*-chlorine atom.

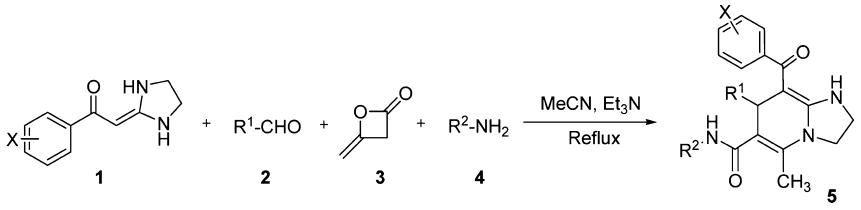
In view of the significance of naphthyridine derivatives,[19] we attempted to use compounds **5s**−**5cc** as the substrates to prepare benzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxamide derivatives. To our delight, we directly used **5t** in the presence of K_2CO_3 in DMF at 100 °C to obtain benzo[*b*]-imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxamide (**6a**) in an excellent yield of 91%.

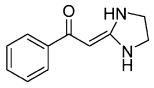
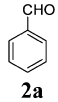
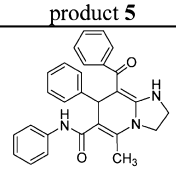
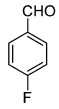
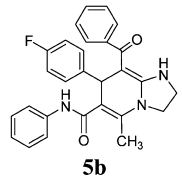
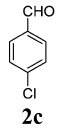
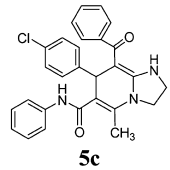
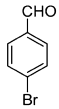
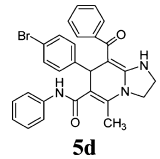
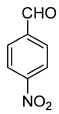
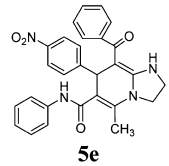
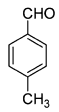
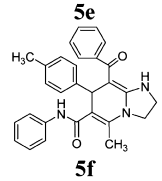
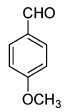
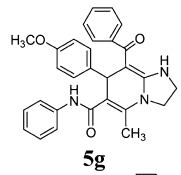
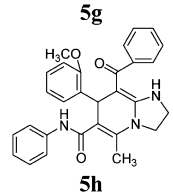
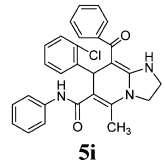
The synthesis of tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridines **6** does not necessarily require the isolation of intermediates **5**. We conducted the preparation of **6a** simply by stirring the mixture of 1-(2,4-dichloro-5-fluorophenyl)-2-(imidazolidin-2-ylidene)ethanone (**1e**), 4-chlorobenzaldehyde (**2c**), diketene (**3**), and phenylamine (**4a**) in refluxing MeCN with 0.5 equiv of Et_3N as the catalyst for 18 h to give the expected **5t**, followed by, after removal of the solvent, stirring the residue with 1 equiv of K_2CO_3 in DMF at 100 °C for about 10 h. The one-pot, two-step process successfully led to the corresponding product **6a** in a good total yield of 81% (Table 3, entry 1).

Inspired by the above results, the reactions of four HKAs (**1d**−**f** and **1g**), six aromatic aldehydes with diketene (**3**) and phenylamine (**4a**) were investigated under the above conditions (Table 3). The desired products **6** were obtained except **6i**, which may be ascribed to the low activity of the *o*-halogen leaving group of the aryl ring without other electron-withdrawing groups. Thus, a stronger base NaH (1 equiv) was chosen as the catalyst for **6i**. To our delight, the reaction

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

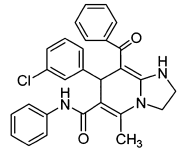
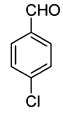
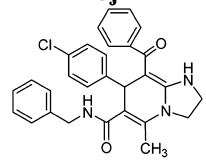
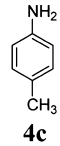
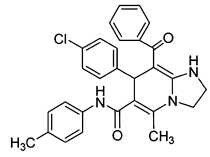
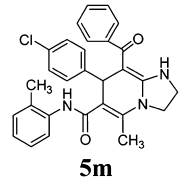
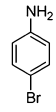
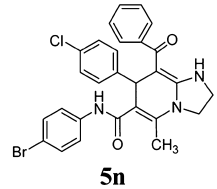
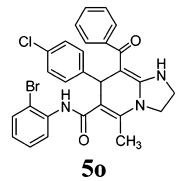
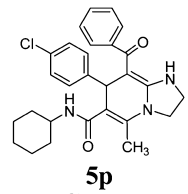
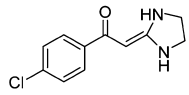
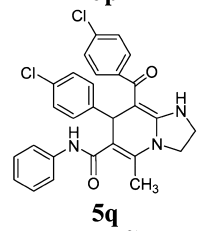
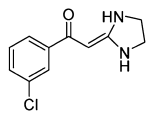
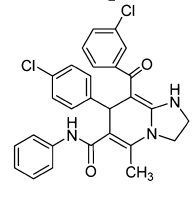
Table 2. One-Pot Four-Component Synthesis of Products 5[a]



entry	precursor **1**	precursor **2**	precursor **4**	product **5**	yield[b] /%
1	 **1a**	 **2a**	 **4a**	 **5a**	73
2	**1a**	 **2b**	**4a**	 **5b**	85
3	**1a**	 **2c**	**4a**	 **5c**	80
4	**1a**	 **2d**	**4a**	 **5d**	76
5	**1a**	 **2e**	**4a**	 **5e**	84
6	**1a**	 **2f**	**4a**	 **5f**	61
7	**1a**	 **2g**	**4a**	 **5g**	55
8	**1a**	 **2h**	**4a**	 **5h**	trace[c]
9	**1a**	 **2i**	**4a**	 **5i**	82

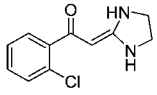
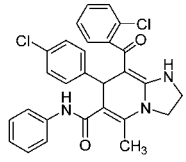
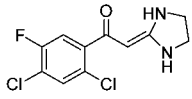
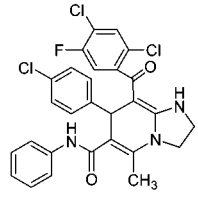
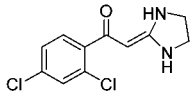
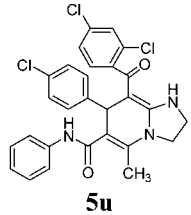
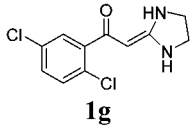
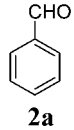
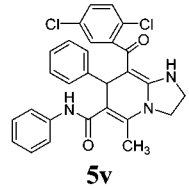
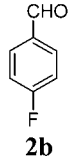
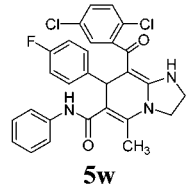
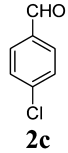
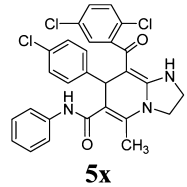
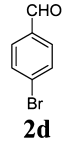
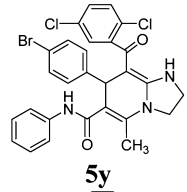
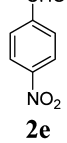
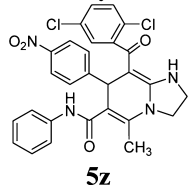
dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

Table 2. continued

entry	precursor **1**	precursor **2**	precursor **4**	product **5**	yield[b] /%
10	**1a**	 **2j**	**4a**	 **5j**	81
11	**1a**	 **2c**	 **4b**	 **5k**	86
12	**1a**	**2c**	 **4c**	 **5l**	77
13	**1a**	**2c**	 **4d**	 **5m**	Trace[c]
14	**1a**	**2c**	 **4e**	 **5n**	51[c]
15	**1a**	**2c**	 **4f**	 **5o**	30[c]
16	**1a**	**2c**	 **4g**	 **5p**	80
17	 **1b**	**2c**	 **4a**	 **5q**	78
18	 **1c**	**2c**	**4a**		80

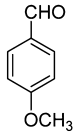
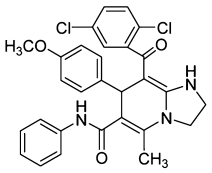
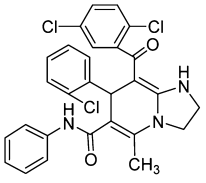
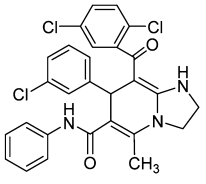
dx.doi.org/10.1021/jo3013836 | *J. Org. Chem.* 2012, 77, 8956−8967

Table 2. continued

entry	precursor **1**	precursor **2**	precursor **4**	product **5**	yield[b] /%
19	 **1d**	**2c**	**4a**	 **5r**	80
20	 **1e**	**2c**	**4a**	 **5s**	89
21	 **1f**	**2c**	**4a**	 **5t**	82
22	 **1g**	 **2a**	**4a**	 **5u**	81
23	**1g**	 **2b**	**4a**	 **5v**	95
24	**1g**	 **2c**	**4a**	 **5w**	85
25	**1g**	 **2d**	**4a**	 **5x**	81
26	**1g**	 **2e**	**4a**	 **5y**	92
				5z	

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

Table 2. continued

entry	precursor **1**	precursor **2**	precursor **4**	product **5**	yield[b] /%
27	**1g**	 **2g**	**4a**	 **5aa**	62
28	**1g**	 **2h**	**4a**	 **5bb**	86
29	**1g**	 **2i**	**4a**	 **5cc**	83

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), **4** (1.0 mmol), Et_3N (0.5 equiv), refluxing MeCN (5 mL), 18 h. [b]Isolated yield. [c]Reation time 30 h.

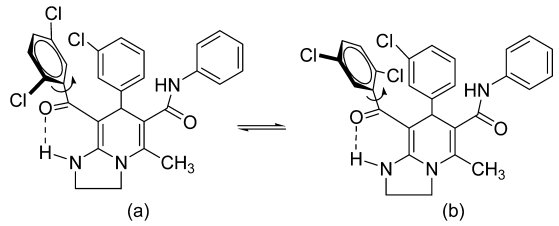


Figure 3. Isomerization results from the rotational barrier.

proceeded smoothly, and **6i** was gained in a yield of 65% (Table 3, entry 9).

The structures of **6a**−**i** were characterized by their IR, NMR, and HRMS spectral data, which are in agreement with the proposed structures. It is worth noting that in all of the ^1H NMR spectra of products **6** there is one set of signals with no unusual splitting peaks, which also further demonstrated the splitting peaks in the ^1H NMR spectra of products **5s**−**5cc** arising from the rotational barrier involving the *o*-chlorine atom.

On the basis of the above results, a plausible mechanism for this reaction was proposed (Scheme 2). First, the attack on the carbonyl group of diketene (**3**) by the amino moiety **4** led to the carboanion [**A**] under Et_3N as the catalyst. Then [**A**] underwent Knoevenagel condensation with **2** to give [**B**]. Next the heterocyclic ketene aminals **1**, as aza−ene reaction components, reacted with intermediates [**B**] to afford intermediates [**C**], which underwent a rapid imine−enamine tautomerization to give intermediates [**D**]. Then an intramolecular cyclization of [**D**] led to the formation of imidazo[1,2-*a*]pyridines **5** with loss of one molecule of H_2O. Finally, the carbon attached to the *o*-chlorine on the aryl group of compounds **5** was attacked by the NH group through S_NAr, leading to the benzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives **6** with elimination of HCl.

CONCLUSION

In summary, we have developed a convenient, efficient synthetic protocol for imidazo[1,2-*a*]pyridines and imidazo-[1,2,3-*ij*][1,8]naphthyridines by four-component domino reactions of HKAs, aldehydes, diketene, and amines using Et_3N as the catalyst. The transformation involving multiple steps and not requiring the use of transition-metal catalysts constructs at least four new bonds with all reactants efficiently being utilized. These studies highlighted the concept of a substrate-design approach and paved an efficient and flexible way to synthesize biologically active imidazo[1,2-*a*]pyridine and imidazo[3,2,1-*ij*][1,8]naphthyridines with structural diversity. Importantly, the unusual splitting peaks in the ^1H NMR spectra of the products derived from heterocyclic ketene aminals with an *o*-halogen atom on the aryl ring were explained reasonably by varying the temperature in NMR analysis. We hope this approach may be of value for other researchers to seek novel synthetic fragments with unique properties for medicinal chemistry.

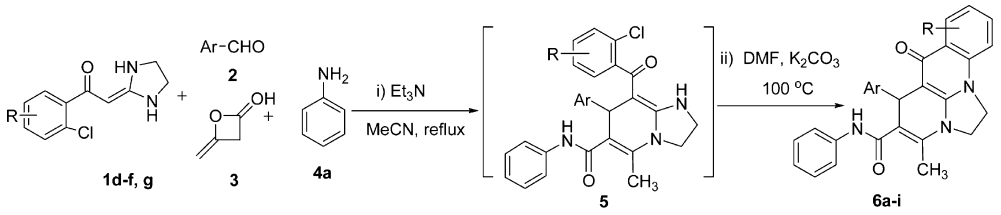
EXPERIMENTAL SECTION

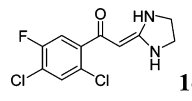
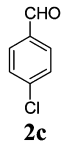
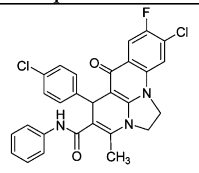
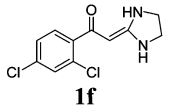
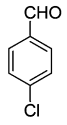
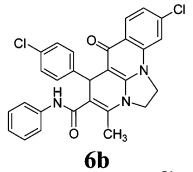
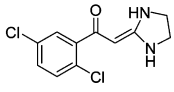
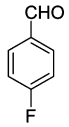
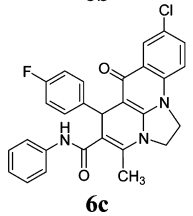
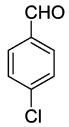
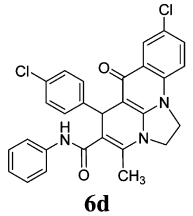
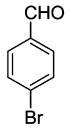
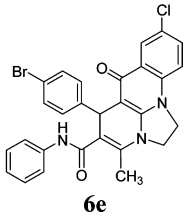
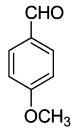
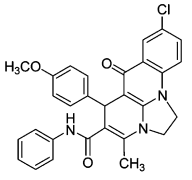
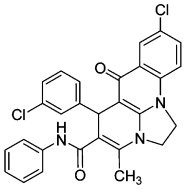
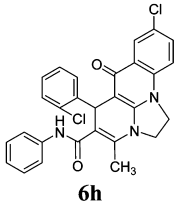
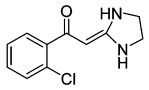
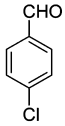
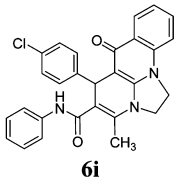
General Procedure for the Preparation of Products 5. A solution of diketene (**3**; 1.0 mmol) and amines **4** (1.0 mmol) was stirred in dry MeCN (5 mL) at room temperature with Et_3N (0.5 mmol) as the catalyst for 10 min. Then heterocyclic ketene aminals **1** (1.0 mmol) and aromatic aldehydes **2** (1.0 mmol) were added, and the mixture was heated to reflux for 18 h. After completion of the reaction as indicated by TLC (petroleum ether−EtOAc, 1:4, v/v), the solvent was removed under vacuum, and the residue was purified by column chromatography (petroleum ether−EtOAc, 1:4, v/v) to afford products **5**.

General Procedure for the Preparation of Products 6. A solution of diketene (**3**; 1.0 mmol) and phenylamine (**4a**; 1.0 mmol) was stirred in dry MeCN (5 mL) at room temperature with Et_3N (0.5 mmol) as the catalyst for 10 min. Then heterocyclic ketene aminals **1** (1.0 mmol) and aromatic aldehydes **2** (1.0 mmol) were added, and the mixture was heated to reflux for 18 h. After completion of the reaction as indicated by TLC (petroleum ether−EtOAc, 1:4, v/v), the solvent

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

Table 3. Synthesis of Products 6 via Tandem Reaction[a]



entry	precursor 1	precursor 2	product 6	yield[b] /%
1	 1e	 2c	 6a	81
2	 1f	 2c	 6b	72
3	 1g	 2b	 6c	85
4	1g	 2c	 6d	73
5	1g	 2d	 6e	72
6	1g	 2g	 6f	60
7	1g	 2i	 6g	69
8	1g	 2h	 6h	70
9[c]	 1d	 2c	 6i	65

[a]Reaction conditions: (i) **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), **4** (1.0 mmol), Et_3N (0.5 equiv), refluxing MeCN (5 mL), 18 h; (ii) K_2CO_3 (1 equiv), DMF (5 mL), 100 °C, 10 h. [b]Total isolated yield of **6** based on **1**. [c]Reaction conditions: NaH (1 equiv), DMF (5 mL), 100 °C, 10 h.

was removed under vacuum. To the residue were added DMF (5 mL) and K_2CO_3 (1 mmol), and the resulting mixture was then heated to 100 °C for 10 h. After completion of the reaction as indicated by TLC (petroleum ether−EtOAc, 1:6, v/v), the mixture was cooled to room temperature. Ice−water was added to precipitate the products, which were then filtered and washed with ethanol to give pure products **6**.

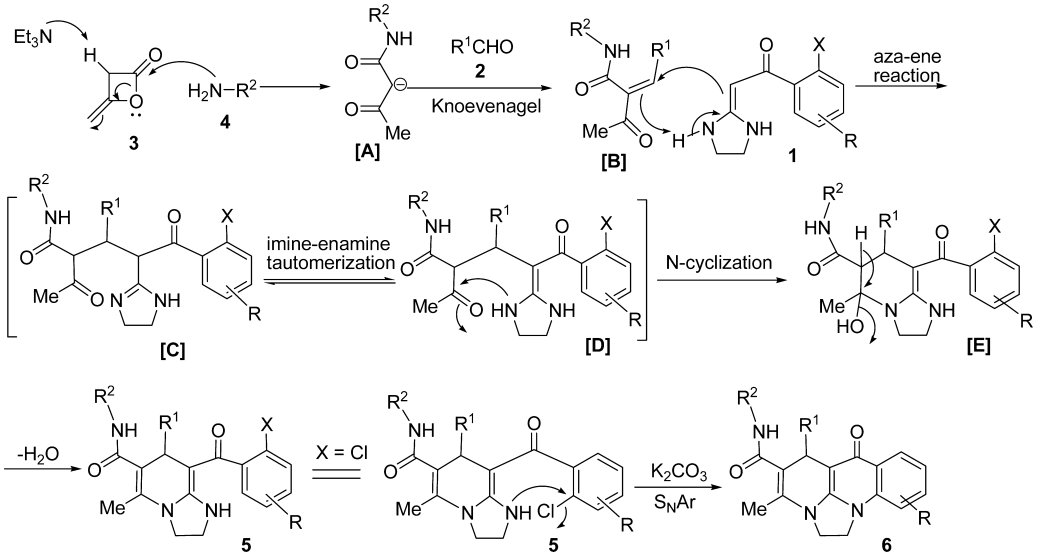
Data for 8-benzoyl-5-methyl-*N*,7-diphenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5a): isolated yield 318 mg (73%); brown powder; mp 243−245 °C; IR (KBr) ν 3272, 1663, 1634, 1598, 1488, 1439, 1289, 1248, 755, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 3H), 3.82−4.02 (m, 4H), 4.71 (s, 1H), 6.69−7.34 (m, 16H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 42.5, 42.6, 45.0, 88.8, 112.1, 112.2, 119.5, 123.9, 126.6, 127.1, 128.2, 128.2, 128.8, 138.0, 138.6, 138.9, 141.9, 146.8, 156.4, 166.8, 192.9; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{26}N_3O_2$ 436.2025, found 436.2032.

Data for 8-benzoyl-7-(4-fluorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5b): isolated yield 385 mg (85%); yellow powder; mp 229−231 °C; IR (KBr) ν 3289, 1660, 1635, 1599, 1504, 1484, 1440, 1289, 1248, 852, 755, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.32 (s, 3H), 3.82−3.99 (m, 4H), 4.73 (s, 1H), 6.64−7.33 (m, 15H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 41.9, 42.6, 45.0, 88.7, 112.4, 115.5 ($^2J_{C-F}$ = 21.1 Hz), 119.6, 124.1, 126.4, 128.3, 128.6, 128.7, 128.9, 137.8, 138.0, 141.8, 142.7, 142.2, 156.4, 161.6 ($^1J_{C-F}$ = 244.4 Hz), 166.8, 192.9; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{25}N_3O_2F$ 454.1931, found 454.1941.

Data for 8-benzoyl-7-(4-chlorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5c): isolated yield 375 mg (80%); light yellow powder; mp 247−249 °C; IR (KBr) ν 3307, 1660, 1600, 1486, 1438, 1289, 1244, 833, 753, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 3H), 3.81−3.99 (m, 4H), 4.72 (s, 1H), 6.62−7.34 (m, 15H), 9.26 (s, 1H); ^{13}C NMR

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

Scheme 2. Plausable Mechanism for the Formation of Compounds 5 and 6



(CDCl$_3$, 125 MHz) δ 16.3, 42.0, 42.7, 45.0, 88.3, 112.2, 119.7, 124.2, 126.4, 128.3, 128.4, 128.8, 128.9, 132.5, 137.8, 138.0, 141.7, 145.3, 156.4, 166.8, 192.8; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{28}H_{25}N_3O_2Cl$ 470.1635, found 470.1645.

Data for 8-benzoyl-7-(4-bromophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5d): isolated yield 390 mg (76%); yellow powder; mp 246−248 °C; IR (KBr) ν 3286, 1655, 1660, 1599, 1482, 1437, 1288, 1248, 832, 753, 702 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.29 (s, 3H), 3.80−3.98 (m, 4H), 4.72(s, 1H), 6.57−7.34 (m, 15H), 9.27 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.2, 42.2, 42.6, 45.0, 88.2, 112.3, 119.7, 120.6, 124.2, 126.4, 128.3, 128.8, 128.9, 131.7, 137.7, 137.8, 141.8, 145.8, 156.5, 166.8, 192.8; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{28}H_{25}N_3O_2Br$ 514.1130, found 514.1125.

Data for 8-benzoyl-5-methyl-7-(4-nitrophenyl)-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5e): isolated yield 403 mg (84%); yellow powder; mp 201−203 °C; IR (KBr) ν 3291, 3288, 1663, 1651, 1604, 1510, 1438, 1290, 1251, 813, 753, 699 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.23 (s, 3H), 3.79−3.94 (m, 4H), 4.96 (s, 1H), 6.87−7.95 (m, 15H), 9.25 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.2, 42.7, 42.9, 44.9, 87.3, 112.6, 119.9, 123.6, 124.4, 126.2, 127.9, 128.3, 129.0, 136.0, 137.6, 141.6, 146.4, 154.2, 156.7, 166.7, 192.5; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{28}H_{25}N_4O_4$ 481.1876, found 481.1889.

Data for 8-benzoyl-5-methyl-*N*-phenyl-7-(*p*-tolyl)-1,2,3,7-tetrahydroimidazo[1,2-*a*] pyridine-6-carboxamide (5f): isolated yield 274 mg (61%); light brown powder; mp 237−239 °C; IR (KBr) ν 3293, 1667, 1637, 1598, 1487, 1439, 1290, 1249, 838, 755, 704 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.27 (s, 3H), 2.35 (s, 3H), 3.80−4.03 (m, 4H), 4.66 (s, 1H), 6.56−7.36 (m, 15H), 9.22 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.3, 21.0, 42.0, 42.6, 45.0, 89.0, 112.1, 119.5, 123.8, 126.7, 126.9, 128.2, 128.8, 129.5, 136.6, 138.2, 139.0, 141.9, 143.8, 156.4, 166.9, 192.8; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{29}H_{28}N_3O_2$ 450.2182, found 450.2172.

Data for 8-benzoyl-7-(4-methoxyphenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5g): isolated yield 256 mg (55%); brown powder; mp 229−231 °C; IR (KBr) ν 3279, 1660, 1632, 1605, 1508, 1485, 1439, 1289, 1244, 829, 754, 706 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.37 (s, 3H), 3.76 (s, 3H), 3.83−4.05 (m, 4H), 4.66 (s, 1H), 6.61−7.36 (m, 15H), 9.25 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.3, 41.6, 42.6, 45.1, 55.2, 89.2, 112.2, 114.2, 119.5, 123.8, 126.6, 128.2, 128.8, 138.1, 138.9, 139.1, 141.9, 156.3, 158.6, 166.9, 192.9; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{29}H_{28}N_3O_3$ 466.2131, found 466.2138.

Data for 8-benzoyl-7-(2-chlorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5i): isolated yield 385 mg (82%); light yellow powder; mp 239−241 °C; IR (KBr) ν 3289, 1667, 1655, 1600, 1487, 1439, 1289, 1251, 753, 702 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.25 (s, 3H), 3.86−4.02 (m, 4H), 5.22 (s, 1H), 6.83−7.29 (m, 15H), 9.38 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.4, 40.1, 42.9, 45.2, 88.1, 112.5, 120.2, 124.4, 126.3, 127.6, 128.1, 128.5, 128.8, 129.0, 129.8, 131.1, 132.3, 136.3, 138.1, 142.2, 144.3, 157.2, 166.9, 193.6; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{28}H_{25}N_3O_2Cl$ 470.1635, found 470.1625.

Data for 8-benzoyl-7-(3-chlorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5j): isolated yield 380 mg (81%); white powder; mp 220−222 °C; IR (KBr) ν 3305, 1663, 1637, 1598, 1482, 1439, 1289, 1248, 754, 702 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.33 (s, 3H), 3.84−4.02 (m, 4H), 4.74 (s, 1H), 6.51−7.37 (m, 15H), 9.30 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.6, 42.7, 42.9, 45.3, 88.4, 112.2, 119.9, 124.4, 125.5, 126.6, 127.3, 127.6, 128.5, 129.1, 130.1, 134.8, 138.0, 138.3, 141.9, 149.0, 156.6, 166.9, 193.1; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{28}H_{25}N_3O_2Cl$ 470.1635, found 470.1642.

Data for 8-benzoyl-*N*-benzyl-7-(4-chlorophenyl)-5-methyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5k): isolated yield 416 mg (86%); white powder; mp 231−233 °C; IR (KBr) ν 3274, 1667, 1619, 1608, 1487, 1453, 1286, 1257, 754, 705 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.23 (s, 3H), 3.79−3.93 (m, 4H), 4.12−4.46 (m, 2H), 4.73 (s, 1H), 5.30 (s, 1H), 6.52−7.33 (m, 14H), 9.22 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.1, 42.3, 42.7, 43.5, 45.0, 88.2, 112.9, 126.4, 127.3, 128.2, 128.5, 128.6, 128.7, 132.1, 135.3, 138.0, 141.9, 145.46, 156.7, 168.6, 192.9; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{29}H_{27}N_3O_2Cl$ 484.1792, found 484.1796.

Data for 8-benzoyl-7-(4-chlorophenyl)-5-methyl-*N*-(*p*-tolyl)-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5l): isolated yield 372 mg (77%); gray powder; mp 235−237 °C; IR (KBr) ν 3285, 1664, 1632, 1605, 1487, 1452, 1287, 1250, 815, 752, 705 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.26 (s, 3H), 2.30 (s, 3H), 3.84−3.99 (m, 4H), 4.71 (s, 1H), 6.62−7.33 (m, 14H), 9.27 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.3, 20.9, 42.1, 42.7, 45.1, 88.4, 112.5, 119.8, 126.5, 128.3, 128.5, 128.8, 128.9, 129.4, 132.5, 133.9, 135.2, 137.6, 141.8, 145.4, 156.6, 166.8, 192.9; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{29}H_{27}N_3O_2Cl$ 484.1792, found 484.1786.

Data for 8-benzoyl-*N*-(4-bromophenyl)-7-(4-chlorophenyl)-5-methyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5n): isolated yield 280 mg (51%); yellow powder; mp 245−247 °C; IR (KBr) ν 3270, 1670, 1606, 1486, 1455, 1285, 1248, 796, 750, 704 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.30 (s, 3H), 3.83−3.99 (m, 4H), 4.70 (s, 1H), 6.60−7.36 (m, 14H), 9.23 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.4, 42.0, 42.7, 45.0, 88.3, 111.7, 116.6, 121.2, 126.4, 128.3, 128.4, 128.9, 129.0, 131.8, 132.6, 136.9, 138.6, 141.7,

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

145.2, 156.3, 166.7, 192.8; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{24}N_3O_2BrCl$ 548.0740, found 548.0749.

Data for 8-benzoyl-*N*-(2-bromophenyl)-7-(4-chlorophenyl)-5-methyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5o): isolated yield 165 mg (30%); yellowgreen powder; mp 145−147 °C; IR (KBr) ν 3417, 1672, 1631, 1518, 1479, 1452, 1290, 1244, 795, 749, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.40 (s, 3H), 3.83−4.04 (m, 4H), 4.87 (s, 1H), 6.65−8.20 (m, 14H), 9.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.4, 41.7, 42.7, 45.1, 88.4, 111.7, 113.7, 122.4, 125.0, 126.7, 128.1, 128.3, 128.3, 128.8, 129.0, 132.1, 132.4, 135.8, 139.3, 141.6, 144.6, 156.4, 166.5, 192.6; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{24}N_3O_2BrCl$ 548.0740, found 548.0736.

Data for 8-benzoyl-7-(4-chlorophenyl)-*N*-cyclohexyl-5-methyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5p): isolated yield 380 mg (80%); brown powder; mp 243−245 °C; IR (KBr) ν 3270, 2931, 2854, 1667, 1615, 1487, 1452, 1287, 1253, 798, 751, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.73−1.72 (m, 10H), 2.17 (s, 3H), 3.62−3.68 (m, 1H), 3.84−3.95 (m, 4H), 4.64 (s, 1H), 4.85 (d, J = 8 Hz, 1H), 6.58−7.32 (m, 10H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.9, 24.5, 25.4, 32.7, 42.4, 42.6, 45.0, 48.0, 88.1, 113.6, 126.4, 128.2, 128.4, 128.6, 128.7, 132.0, 133.8, 141.9, 145.6, 156.8, 167.9, 192.9; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{31}N_3O_2Cl$, 476.2105 found 476.2115.

Data for 8-(4-chlorobenzoyl)-7-(4-chlorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5q): isolated yield 392 mg (78%); yellow powder; mp 165−167 °C; IR (KBr) ν 1667, 1637, 1597, 1486, 1440, 1289, 1252, 757, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 3H), 3.86−4.01 (m, 4H), 4.66(s, 1H), 6.68−7.28 (m, 14H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 42.2, 42.7, 45.1, 88.2, 112.6, 119.8, 124.3, 128.0, 128.4, 128.5, 129.0, 132.8, 134.8, 137.3, 137.7, 140.2, 145.3, 156.7, 166.7, 191.4; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{24}N_3O_2Cl_2$ 504.1246, found 504.1256.

Data for 8-(3-chlorobenzoyl)-7-(4-chlorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5r): isolated yield 402 mg (80%); yellow powder; mp 150−152 °C; IR (KBr) ν 3282, 1667, 1637, 1596, 1485, 1439, 1289, 1251, 757, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 3H), 3.84−4.03 (m, 4H), 4.66 (m, 1H), 6.68−7.28 (m, 14H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 42.1, 42.7, 45.1, 88.2, 112.7, 119.8, 124.3, 128.0, 128.4, 128.5, 129.0, 132.7, 134.8, 137.1, 137.7, 140.1, 145.2, 156.7, 166.7, 191.3; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{24}N_3O_2Cl_2$ 504.1246, found 504.1256.

Data for 8-(2-chlorobenzoyl)-7-(4-chlorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5s): isolated yield 402 mg (80%); brown powder; mp 210−212 °C; IR (KBr) ν 3276, 1665, 1663, 1604, 1488, 1436, 1290, 1254, 838, 755, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 3H), 3.85−3.98 (m, 4H), 4.40 (s, 1H), 6.62−7.35 (m, 14H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 42.2, 42.8, 45.0, 88.9, 113.3, 119.6, 124.2, 126.8, 128.6, 128.9, 129.2, 129.4, 130.1, 132.4, 136.3, 136.7, 137.8, 140.2, 140.6, 145.3, 156.7, 166.8, 189.2; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{24}N_3O_2Cl_2$ 504.1246, found 504.1241.

Data for 7-(4-chlorophenyl)-8-(2,4-dichloro-5-fluorobenzoyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]-pyridine-6-carboxamide (5t): isolated yield 494 mg (89%); green powder; mp 186−188 °C; IR (KBr) ν 1667, 1663, 1598, 1488, 1439, 1289, 1254, 836, 756, 722, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.22 (s, 3H), 3.88−4.03 (m, 4H), 4.37 (s, 1H), 6.30−7.42 (m, 12H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 42.3, 42.8, 45.1, 88.6, 113.9, 117.2, 119.8, 121.5 ($^2J_{C-F}$ = 19.0 Hz), 124.4, 128.7, 128.8, 129.0 131.1, 132.9, 135.1, 137.6, 140.5, 145.2, 156.6 ($^1J_{C-F}$ = 250.0 Hz), 157.1, 166.6, 186.5; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2Cl_3F$ 556.0762, found 556.0775.

Data for 7-(4-chlorophenyl)-8-(2,4-dichlorobenzoyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5u): isolated yield 440 mg (82%); gray powder; mp 176−178 °C; IR (KBr) ν 3293, 1667, 1663, 1601, 1486, 1438, 1290, 1254, 827, 757, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 3H), 3.88−4.03 (m, 4H), 4.39 (s, 1H), 6.51−7.39 (m, 13H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 42.2, 42.8, 45.0, 88.9, 113.5, 119.7, 124.3, 127.1, 127.7, 128.7, 129.0, 129.8, 130.2, 132.7, 134.5, 136.0, 137.6, 145.3, 156.8, 166.7, 187.9; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl_3$ 538.0856, found 538.0867.

Data for 8-(2,5-dichlorobenzoyl)-5-methyl-*N*,7-diphenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5v): isolated yield 407 mg (81%); light yellow powder; mp 221−223 °C; IR (KBr) ν 3277, 1688, 1652, 1600, 1440, 1289, 1253, 823, 754, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3H), 3.85−4.03 (m, 4H), 4.28 (s, 1H), 6.39−7.29 (m, 14H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.4, 42.8, 45.1, 89.5, 113.6, 119.7, 124.1, 127.5, 129.0, 129.5, 130.5, 132.6, 136.4, 137.9, 142.1, 146.9, 156.9, 166.9, 187.5; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{24}N_3O_2Cl_2$ 504.1246, found, 504.1256.

Data for 8-(2,5-dichlorobenzoyl)-7-(4-fluorophenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5w): isolated yield 495 mg (95%); green powder; mp 236−238 °C; IR (KBr) ν 3277, 1671, 1652, 1600, 1505, 1491, 1441, 1290, 1254, 795, 756, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H, CH_3), 3.84−3.99 (m, 4H), 4.33 (s, 1H), 6.39−7.26 (m, 13H,), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 42.0, 42.8, 45.1, 89.2, 113.8, 115.5 ($^2J_{C-F}$ = 21.1 Hz), 119.7, 124.3, 126.7, 127.3, 129.0, 130.5, 132.6, 135.5, 137.7, 142.0, 142.8, 156.9, 161.8 ($^1J_{C-F}$ = 244.8 Hz), 166.8, 187.5; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl_2F$ 522.1151, found, 522.1162.

Data for 7-(4-chlorophenyl)-8-(2,5-dichlorobenzoyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5x): isolated yield 456 mg (85%); light green powder; mp 211−213 °C; IR (KBr) ν 3258, 1668, 1636, 1595, 1483, 1440, 1290, 1258, 819, 754, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3H), 3.85−4.00 (m, 4H), 4.34 (s, 1H), 6.40−7.27 (m, 13H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 42.3, 42.8, 45.0, 88.8, 113.7, 119.8, 124.3, 127.2, 128.7, 128.9, 129.2, 130.4, 132.6, 132.8, 135.2, 137.6, 141.9, 145.4, 156.9, 166.7, 187.5; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl_3$ 538.0856, found 538.0862.

Data for 7-(4-bromophenyl)-8-(2,5-dichlorobenzoyl)-5-methyl-*N*-phenyl-1,2,3,7- tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5y): isolated yield 471 mg (81%); light yellow powder; mp 224−236 °C; IR (KBr) ν 3277, 1668, 1636, 1596, 1483, 1439, 1290, 1252, 819, 754, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3H), 3.86−4.01 (m, 4H), 4.33 (s, 1H), 6.40−7.29 (m, 13H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 42.2, 42.8, 45.0, 88.8, 113.6, 119.7, 120.8, 124.3, 127.2, 129.0, 129.2, 130.4, 131.7, 132.7, 135.3, 137.6, 141.8, 145.9, 156.9, 166.7, 187.4; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl_2Br$ 582.0351, found 582.0358.

Data for 8-(2,5-dichlorobenzoyl)-5-methyl-7-(4-nitrophenyl)-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5z): isolated yield 504 mg (92%); brown powder; mp 216−218 °C; IR (KBr) ν 3270, 1670, 1630, 1609, 1518, 1488, 1440, 1290, 1243, 821, 763, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 3H), 3.93−4.06 (m, 4H), 4.59 (s, 1H), 6.34−8.01 (m, 13H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 42.9, 45.1, 87.9, 113.6, 119.9, 123.7, 124.7, 127.3, 128.2, 129.1, 129.5, 130.6, 132.8, 134.5, 137.4, 141.8, 146.6, 154.0, 157.0, 166.4, 187.5; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_4O_4Cl_2$ 549.1096, found 549.1085.

Data for 8-(2,5-dichlorobenzoyl)-7-(4-methoxyphenyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5aa): isolated yield 330 mg (62%); white powder; mp 188−190 °C; IR (KBr) ν 3309, 1672, 1632, 1608, 1487, 1440, 1290, 1240, 820, 762, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.27 (s, 3H), 3.80 (s, 3H), 3.85−4.04 (m, 4H), 4.23 (s, 1H), 6.42−7.30 (m, 13H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6, 37.0, 38.0, 40.4, 50.7, 85.1, 108.9, 109.5, 114.9, 119.3, 123.8, 124.2, 124.4, 124.8, 125.7, 127.8, 133.2, 134.4, 152.0, 154.0, 162.2, 182.8; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{29}H_{26}N_3O_3Cl_2$ 534.1351, found 534.1342.

Data for 7-(2-chlorophenyl)-8-(2,5-dichlorobenzoyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5bb): isolated yield 462 mg (86%); yellow powder; mp 242−244 °C; IR (KBr) ν 3277, 1673, 1662, 1609, 1491, 1440,

dx.doi.org/10.1021/jo3013836 | J. Org. Chem. 2012, 77, 8956−8967

1289, 1251, 815, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.14 (s, 3H), 3.86−4.00 (m, 4H), 4.95 (s, 1H), 6.18−7.28 (m, 13H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 39.2, 42.8, 45.0, 88.9, 113.2, 120.0, 124.3, 127.0, 127.6, 128.1, 128.4, 128.9, 129.2, 130.5, 130.9, 131.3, 132.6, 134.1, 137.8, 142.1, 144.0, 157.4, 166.4, 187.7; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl_3$ 538.0856, found 538.0862.

Data for 7-(3-chlorophenyl)-8-(2,5-dichlorobenzoyl)-5-methyl-*N*-phenyl-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide (5cc): isolated yield 446 mg (83%); light green powder; mp 240−242 °C; IR (KBr) ν 3213, 1667, 1644, 1596, 1495, 1438, 1286, 1254, 829, 747, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 3.92−4.05 (m, 4H), 4.35 (s, 1H), 6.42−7.28 (m, 13H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 42.8, 45.0, 88.8, 113.4, 119.8, 124.3, 125.5, 127.3, 127.6, 127.9, 129.0, 129.4, 129.8, 130.5, 131.2, 132.7, 134.7, 135.7, 137.6, 142.0, 148.8, 156.8, 166.6; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl_3$ 538.0856, found 538.0868.

Data for 10-chloro-6-(4-chlorophenyl)-9-fluoro-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*]-[1,8]naphthyridine-5-carboxamide (6a): isolated yield 420 mg (81%); white powder; mp 258−260 °C; IR (KBr, cm^{-1}) 3254, 1672, 1647, 1590, 1521, 1428, 1293, 1233, 766, 753, 694; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.18 (s, 3H), 4.15−4.49 (m, 4H), 5.31 (s, 1H), 6.98−7.76 (m, 11H), 9.82 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.8, 45.4, 45.8, 97.6, 112.3 ($^2J_{C-F}$ = 24.3 Hz), 117.6, 120.2, 123.7, 125.2, 128.2, 129.0, 130.2, 131.1, 134.4, 135.8, 139.6, 144.8, 148.4, 153.3 ($^1J_{C-F}$ = 241.1 Hz), 167.3, 172.2; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{21}N_3O_2FCl_2$ 520.0995, found 520.0986.

Data for 10-chloro-6-(4-chlorophenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6b): isolated yield 361 mg (72%); white powder; mp 263−265 °C; IR (KBr) ν 3256, 1668, 1615, 1596, 1523, 1436, 1296, 1246, 780, 756, 694 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.19 (s, 3H), 4.13−4.46 (m, 4H), 5.32 (s, 1H), 7.01−7.94 (m, 12H), 9.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.8, 21.2, 45.4, 60.2, 79.6, 97.8, 112.2, 114.9, 120.3, 122.7, 123.7, 123.9, 128.0, 128.2, 129.0, 130.2, 131.0, 135.8, 136.5, 138.3, 139.6, 145.0, 148.3, 167.4, 170.9, 173.1; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2Cl_2$ 502.1089, found 502.1092.

Data for 9-chloro-6-(4-fluorophenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6c): isolated yield 412 mg (85%); yellow powder; mp 193−195 °C; IR (KBr) ν 3262, 1668, 1645, 1597, 1521, 1440, 1219, 762, 717 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.21 (s, 3H), 4.20−4.51 (m, 4H), 5.35 (s, 1H), 7.00−7.91 (m, 12H), 9.79 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.9, 44.3, 98.6, 111.9, 114.5 ($^2J_{C-F}$ = 20.8 Hz), 114.8, 119.5, 123.2, 125.3, 125.7, 127.6, 128.1, 129.0, 130.8, 134.6, 135.7, 138.3, 140.0, 147.0, 161.0 ($^1J_{C-F}$ = 242.9 Hz), 166.6, 172.6; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2ClF$ 486.1385, found 486.1392.

Data for 9-chloro-6-(4-chlorophenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6d): isolated yield 366 mg (73%); gray powder; mp 205−207 °C; IR (KBr) ν 3256, 1668, 1616, 1596, 1521, 1441, 756, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.45 (s, 3H), 4.04−4.22 (m, 4H), 5.29 (s, 1H), 6.90−8.18 (m, 12H), 8.34 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ15.8, 45.4, 97.9, 112.1, 117.6, 120.2, 123.7, 125.0, 126.4, 127.2, 128.2, 129.0, 130.2, 131.6, 136.1, 139.7, 145.0, 148.2, 167.4, 172.4; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2Cl_2$ 502.1089, found 502.1096.

Data for 6-(4-bromophenyl)-9-chloro-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6e): isolated yield 392 mg (72%); yellow powder; mp 218−220 °C; IR (KBr) ν 3270, 1667, 1616, 1596, 1521, 1441, 756, 692 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.21 (s, 3H), 4.19−4.50 (m, 4H), 5.34 (s, 1H), 7.00−7.89 (m, 12H), 9.84 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.8, 45.5, 97.9, 112.1, 117.6, 119.6, 120.3, 123.7, 125.0, 126.5, 127.2, 129.0, 130.6, 131.1, 131.6, 135.9, 136.1, 139.7, 145.4, 148.2, 167.4, 172.4; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2BrCl$ 546.0584, found 546.0589.

Data for 9-chloro-6-(4-methoxyphenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6f): isolated yield 298 mg (60%); light yellow powder; mp 255−257 °C; IR (KBr) ν 3256, 1674, 1651, 1595, 1519, 1437, 751, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.24 (s, 3H), 3.67 (s, 3H), 4.19−4.55 (m, 4H), 5.33 (s, 1H), 6.75−7.93 (m, 12H), 9.84 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.7, 45.4, 55.4, 98.7, 112.9, 113.7, 117.5, 120.2, 123.6, 125.0, 126.6, 127.1, 129.0, 129.3, 131.4, 135.5, 136.0, 138.4, 139.8, 148.1, 158.0, 167.6, 172.4; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{29}H_{25}N_3O_3Cl$ 498.1584, found 498.1573.

Data for 9-chloro-6-(3-chlorophenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6g): isolated yield 346 mg (69%); light yellow powder; mp 248−250 °C; IR (KBr) ν 3274, 1667, 1616, 1596, 1521, 1440, 1253, 1220, 755, 694 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.20 (s, 3H), 4.14−4.48 (m, 4H), 5.35 (s, 1H), 7.02−7.91 (m, 12H), 9.85 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.7, 45.4, 97.6, 111.8, 117.5, 120.3, 123.6, 125.0, 126.4, 127.0, 127.2, 128.0, 128.9, 130.0, 131.5, 133.0, 136.0, 139.6, 148.2, 148.3, 167.2, 172.4; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2Cl_2$ 502.1089, found 502.1096.

Data for 9-chloro-6-(2-chlorophenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6h): isolated yield 351 mg (70%); yellow powder; mp 250−252 °C; IR (KBr) ν 3278, 3241, 1668, 1617, 1597, 1522, 1440, 1256, 756, 692 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.10 (s, 3H), 4.09−4.45 (m, 4H), 5.73 (s, 1H), 6.94−7.85 (m, 12H), 9.96 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.4, 45.2, 45.5, 98.4, 112.6, 117.5, 120.2, 123.5, 125.0, 126.4, 127.2, 127.5, 128.0, 128.9, 129.2, 131.5, 131.8, 132.6, 134.3, 136.2, 139.8, 143.9, 148.6, 167.0, 172.2; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{22}N_3O_2Cl_2$ 502.1089, found 502.1096.

Data for 6-(4-chlorophenyl)-4-methyl-7-oxo-*N*-phenyl-1,2,6,7-tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]-naphthyridine-5-carboxamide (6i): isolated yield 304 mg (65%); light yellow powder; mp 257−259 °C; IR (KBr) ν 1666, 1617, 1597, 1578, 1521, 1249, 756, 693 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.19 (s, 3H), 4.10−4.45 (m, 2H), 5.35 (s, 1H), 7.00−7.98 (m, 13H), 9.91 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.5, 50.0, 50.1, 102.3, 116.8, 119.9, 125.0, 127.2, 128.4, 130.0, 130.7, 132.9, 133.7, 134.9, 135.7, 136.5, 140.7, 142.1, 144.5, 150.0, 152.6, 172.3, 178.5; HRMS (ESI-TOF, $[M + H]^+$) m/z calcd for $C_{28}H_{23}N_3O_2Cl$ 468.1479, found 468.1485.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General materials and methods, optimization of reaction conditions for the synthesis of **6a** from **5t**, X-ray structure of compound **5cc**, ^1H NMR study for the influence of *o*-chlorine, ^1H and ^{13}C NMR spectra of all new compounds, and X-ray data for compound **5cc** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liming928@qust.edu.cn; wenlirong@qust.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (Grants 20872074 and 21072110) and the Natural Science Foundation of Shandong Province (Grants ZR2010BM007 and ZR2012BM003).

REFERENCES

(1) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61−72.

(2) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743−2746.

(3) Kim, O.; Jeong, Y.; Lee, H.; Hong, S.-S.; Hong, S. *J. Med. Chem.* **2011**, *54*, 2455−2466.

(4) Harrison, T. S.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65−89.

(5) Trabanco, A. A.; Tresadern, G.; Macdonald, G. J.; Vega, J. A.; Lucas, A. I.; de; Matesanz, E.; García, A.; Linares, M. L.; de Diego, S. A. A.; Alonso, J. M.; Oehlrich, D.; Ahnaou, A.; Drinkenburg, W.; Mackie, C.; Andrés, J. I.; Lavreysen, H.; Cid, J. M. *J. Med. Chem.* **2012**, *55*, 2688−2701.

(6) Rether, J.; Erkel, G.; Anke, T.; Bajtnerb, J.; Sterner, O. *Bioorg. Med. Chem.* **2008**, *16*, 1236−1241.

(7) Zhang, W.-W.; Chen, Y.-B.; Chen, W.-D.; Liu, Z.-W.; Li, Z. *J. Agric. Food Chem.* **2010**, *58*, 6296−6299.

(8) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170−1176.

(9) (a) Kazuo, K.; Noriki, I.; Isao, S.; Yasuo, I.; Hiroshige, H.; Masuo, M. U.S. Patent 4186200, 1978. (b) Frohn, M. J.; Hong, F.-T.; Liu, L.; Lopez, P.; Siegmund, A. C.; Tadesse, S.; Tamayo, N. Patent WO 2005070932, 2005. (c) Alonso-Alija, C.; Michels, M.; Schirok, H.; Schlemmer, K.-H.; Dodd, S.; Fitzgerald, M.; Bell, J.; Gill, A. Patent WO 2003053967, 2003. (d) Cheng, D.; Croft, L.; Abdi, M.; Lightfoot, A.; Gallagher, T. *Org. Lett.* **2007**, *9*, 5175−5178.

(10) Bartholini, G. L. E. R. S. *Monogr. Ser.* **1993**, *8*, 1; *Chem. Abstr.* **1996**, *124*, 164079n.

(11) (a) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463−472. (b) Zhu, J.-P.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005, 1499. (c) Isambert, N.; Lavilla, R. *Chem.—Eur. J.* **2008**, *14*, 8444−8454. (d) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040−11041. (e) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149−3159. (f) Fu, H.-Y.; Chen, L.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473−4478. (g) Shao, Na; Pang, G.-X.; Yan, C.-X.; Shi, G.-F.; Cheng, Y. *J. Org. Chem.* **2011**, *76* (18), 7458−7465. (h) Yan, R.-L.; Yan, H.; Ma, C.; Ren, Z.-Y.; Gao, X.-A.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 2024−2028. (i) Wei, H.-L.; Yan, Z.-Y.; Niu, Y.-L.; Li, G.-Q.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 8600−8603. (j) Panda, K.; Suresh, J. R.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3498−3506.

(12) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (c) Zhou, H.-Y.; Zhang, W.; Yan, B. *J. Comb. Chem.* **2010**, *12*, 206−214. (d) Basso, A.; Banfi, L.; Riva, R. *Eur. J. Org. Chem.* **2010**, *75*, 1831−1841. (e) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G.-G. *Chem.—Asian J.* **2010**, *5*, 2318−2335. (f) Lin, X.-F.; Mao, Z.-J.; Dai, X.-X.; Lu, P.; Wang, Y.-G. *Chem. Commun.* **2011**, *47*, 6620−6622. (g) Hong, D.; Zhu, Y.-X.; Li, Y.; Lin, X.-F.; Lu, P.; Wang, Y.-G. *Org. Lett.* **2011**, *13* (17), 4668−4671. (h) Bonne, D.; Dekhane, M.; Zhu, J.-P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485−2488.

(13) (a) Barry, B. T.; Dennis, G. H. *Chem. Rev.* **2009**, *109*, 4439−4486. (b) Kumaravel, K.; Vasuki, G. *Green Chem.* **2009**, *11*, 1945−1947. (c) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G.-G. *J. Am. Chem. Soc.* **2009**, *131*, 11660−11661. (d) Candeias, N. R.; Veiros, L. F.; Afonso, C. A. M.; Gois, P. M. P. *Eur. J. Org. Chem.* **2009**, 1859−1863. (e) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G.-G. *Green Chem.* **2010**, *12*, 1357−1361. (f) Cheng, C.; Jiang, B.; Tu, S.-J.; Li, G.-G. *Green Chem.* **2011**, *13*, 2107−2115.

(14) (a) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.; Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. *J. Org. Chem.* **2004**, *69*, 188−191. (b) Huang, Z.-T.; Wang, M.-X. *Heterocycles* **1994**, *37*, 1233−1262. (c) Wang, M.-X.; Huang, Z.-T. *Prog. Nat. Sci.* **1999**, *9*, 971−983 (in Chinese).

(15) (a) Yu, F.-C.; Yan, S.-J.; Hu, L.; Wang, Y.-C.; Lin, J. *Org. Lett.* **2011**, *13* (18), 4782−4785. (b) Yan, S.-J.; Chen, Y.-L.; Liu, L.; He, N.-Q.; Lin, J. *Green Chem.* **2010**, *12*, 2043−2052. (c) Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **1992**, *57*, 184−190. (d) Xu, Z.-H.; Jie, Y.-F.; Wang, M.-X.; Huang, Z.-T. *Synthesis* **2002**, *4*, 523−527. (e) Wang, M.-X.; Miao, W.-S.; Cheng, Y.; Huang, Z.-T. *Tetrahedron* **1999**, *55*, 14611−14622. (f) Schirok, H.; Alonso-Alijia, C.; Benet-Buchnolz, J.; Goller, A. H.; Grosseor, R.; Michels, M.; Paulsen, H. *J. Org. Chem.* **2005**, *70*, 9463−9469. (g) Chakrabarti, S.; Panda, K.; Misra, N. C.; Ila, H.; Junjappa, H. *Synlett* **2005**, *9*, 1437−1441. (h) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, *12*, 1835−1840. (i) Liao, J.-P.; Zhang, T.; Yu, C.-Y.; Huang, Z.-T. *Synlett* **2007**, *5*, 761−764. (j) Yaqub, M.; Yu, C.-Y.; Jia, Y. M.; Huang, Z.-T. *Synlett* **2008**, *9*, 1357−1360. (k) Yan, S.- J.; Niu, Y.- F.; Huang, R.; Lin, J. *Synlett* **2009**, *17*, 2821−2824. (l) Yan, S.-J.; Huang, C.; Su, C.-X.; Ni, Y.-F.; Lin, J. *J. Comb. Chem.* **2010**, *12*, 91−94. (m) Yu, F.-C.; Yan, S.-J.; Huang, R; Tang, Y.-J.; Lin, J. *RSC Adv.* **2011**, *1*, 596−601.

(16) (a) Clarke, P. A.; Zaytsev, A. V.; Morgan, T. W.; Whitwood, A. C.; Wilson, C. *Org. Lett.* **2008**, *10* (13), 2877−2880. (b) Zeng, L.-Y.; Cai, C. *Org. Biomol. Chem.* **2010**, *8*, 4803−4805. (c) Niu, T.-F.; Gu, L.; Yi, W.-B.; Cai, C. *ACS Comb. Sci.* **2012**, *14*, 309−315. (d) Shaabani, A.; Seyyedhamzeh, M.; Maleki, A.; Rezazadeh, F.; Behnam, M. *J. Comb. Chem.* **2009**, *11*, 375−377. (e) Shaabani, A.; Maleki, A.; Hajishaabanha, F.; Mofakham, H.; Seyyedhamzeh, M.; Mahyari, M.; Ng, S. W. *J. Comb. Chem.* **2010**, *12*, 186−190. (f) Alizadeh, A.; Zohreh, N.; Zhu, L.-G. *Synthesis* **2009**, *3*, 464−468. (g) Alizadeh, A.; Babaki, M.; Zohreh, N. *Synthesis* **2008**, *20*, 3295−3298. (h) Pokhodylo, N. T.; Matiychuk, V. S.; Obushak, M. D. *J. Comb. Chem.* **2009**, *11*, 481−485.

(17) (a) Wen, L.-R.; Li, Z.-R.; Li, M.; Cao, H. *Green Chem.* **2012**, *14* (3), 707−716. (b) Li, M.; Zhou, Z.-M.; Wen, L.-R.; Qiu, Z.-X. *J. Org. Chem.* **2011**, *76*, 3054−3063. (c) Wen, L.-R.; Liu, C.; Li, M.; Wang, L.-J. *J. Org. Chem.* **2010**, *75*, 7605−7614.

(18) (a) Wen, L.-R.; Shi, Y.-J.; Liu, G.-Y.; Li, M. *J. Org. Chem.* **2012**, *77*, 4252−4260. (b) Li, M.; Hou, Y.-L.; Wen, L.-R.; Gong, F.-M. *J. Org. Chem.* **2010**, *75*, 8522−8532. (c) Wen, L.-R.; Sun, J.-H.; Li, M.; Sun, E.-T.; Zhang, S.-S. *J. Org. Chem.* **2008**, *73*, 1852−18631. (d) Wen, L.-R.; Ji, C.; Li, Y.-F.; Li, M. *J. Comb. Chem.* **2009**, *11*, 799−805. (e) Li, M.; Cao, H.; Wang, Y.; Lv, X.-L.; Wen, L.-R. *Org. Lett.* **2012**, *14*, 3470−3473.

(19) (a) Ren, P.; Zhang, G.; You, S.; Sim, T.; Gray, N.; Xie, Y.; Wang, X.; He, Y. WO 136 465, 2007; *Chem. Abstr.* **2007**, *148*, 33755. (b) Cosford, N. D. P.; Layton, M. E.; Liang, J.; Lindsley, C. W.; Sanderson, P. E.; Zhao, Z. WO 091 395, 2006; *Chem. Abstr.* **2006**, *145*, 293099. (c) Wang, Y.; Mull, E. S. WO 101 988, 2003; *Chem. Abstr.* **2006**, *140*, 16716. (d) Shimamoto, T.; Inoue, H.; Hayashi, Y. WO 07 704, 1999; *Chem. Abstr.* **1999**, *130*, 196577. (e) Leach, C. A.; Smith, S. A. WO 086 400, 2003; *Chem. Abstr.* **2003**, *139*, 337978.