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Application of 2-(2-chloroaroyl)methyleneimidazolidines in domino and multicomponent reaction: new entries to imidazo[1,2-*a*]pyridines and benzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines

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Multicomponent reaction

ABSTRACT

A new strategy for the synthesis of tetrahydroimidazo[1,2-*a*]pyridines and unusual tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines has been successfully developed by cascade reactions including Knoevenagel condensation, aza–ene reaction, imine–enamine tautomerization, cyclocondensation/oxidation, and intramolecular S_NAr of precursors 2-(2-chloroaroyl)methyleneimidazolidines as new heterocyclic ketene aminals (HKA), which represent a class of polyfunctional scaffolds with four active reaction sites with aromatic aldehydes and malononitrile or ethyl 2-cyanoacetate under mild conditions. In this domino reaction, nine different active sites are involved, and two C–C bonds, two C–N bonds, and two new rings are constructed with all reactants efficiently utilized in the chemical transformation.

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1. Introduction

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,[1] polyhalo isophthalonitrile,[2] propiolic acid ester,[3] aryl azides,[4] Meldrum's acid and aldehydes,[5] bis(methylthio)methylene malononitrile,[6] itaconic anhydride,[7] α-bromoketones,[8] ethyl 2-(bromomethyl)benzoate,[9] Baylis–Hillman acetates,[10] diethyl azodicarboxylate,[11] 1,3-dibromopropane[12] have so far been successfully adopted to give five-, six-membered and fused heterocycles during the past years. 2-(2-Chloroaroyl)methyleneimidazolidines **2**, as a novel class of HKA with four active sites, show promising structural feature as versatile building blocks for (1) two nucleophilic centers localized on the heteroatoms (two nitrogen atoms); (2) a potential third nucleophilic center of the α-carbon; (3) halogen atom as potential leaving group on the aromatic ring, which subjected to an intramolecular S_NAr reaction. To the best of our knowledge, 2-(2-chloroaroyl)methyleneimidazolidines **2** have never been explored (Fig. 1).

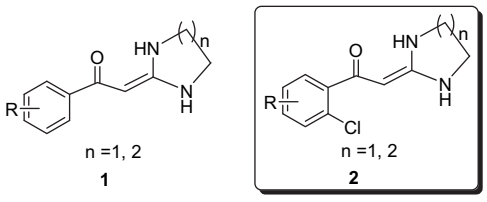

Fig. 1. Functionalized ketene acetals.

In recent years, MCRs have received considerable attention from the organic community due to their advantages over conventional multistep synthesis. The notable feature of MCRs is that new bonds and new functionalities are constructed during the cascade, which, in turn, reacts further in subsequent steps to form new bonds and functionalities until termination leads to desirable molecules. In addition, MCRs are more environmentally benign and atom economic as they avoid time-consuming and costly purification processes, as well as protection-deprotection steps. In this regard, the development of new MCRs is very important in the fields of organic and medicinal chemistry.[13]

Carbon–carbon and carbon–heteroatom bond-forming reactions are central to organic synthesis. The synthesis of heterocycles often involves ene reaction. In 1943, Aider[14] systematically described a σ-bond formation from the reaction between an ene component and an enophile with a concomitant 1,5-hydrogen shift and migration of the double bond. Due to its synthetic potential in organic chemistry, since then, the ene reaction has received much attention and great development has been achieved particularly in

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the past three decades.[15] It has recently been extended by Huang[16] who has explored the aza–ene reactions of heterocyclic ketene aminals utilizing a wide range of enophiles.

Among the nitrogen heterocycles, 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.[17] They have been found in the applications as antibacterial,[18] anti-HIV,[19] antischizophrenia,[20] antiasthma,[21] anti-inflammatory,[22] antihypertensive,[23] anticancer activities.[24] Therefore, the synthesis of imidazo[3,2,1-*ij*][1,8]naphthyridine derivatives may be of great significance.

As a continuation of our interest in the development of MCRs,[25] herein, by simply incorporating an *ortho*-halo group into the aryl ring of 2-benzoylmethyleneimidazolidine, we report the first precursors **2** and their application as highly efficient reagents to develop a new strategy for the synthesis of imidazo[1,2-*a*]pyridine and benzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives in good yields. As far as we know, these compounds are scarcely studied and only two similar examples were reported in the literatures.[16,26] 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.

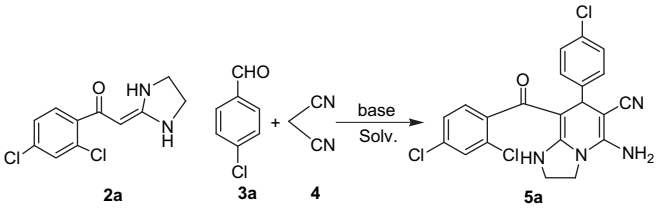
2. Results and discussion

The aza–ene type reaction was initiated by three-component reaction of the precursor 2-(2,4-dichlorophenyl) methyleneimidazolidine **2a** with 4-chlorobenzaldehyde **3a** and malononitrile **4** leading to tetrahydroimidazo[1,2-*a*]pyridine **5a**. Tetrahydroimidazo[1,2-*a*]pyridines motifs are of general interest within medicinal chemistry with therapeutic properties, and a series of substituted variants of **1** (n=1, 2) have been reported as a basis for anticancer,[2] analgesics, and anti-inflammatory agents.[27] As a result of the utility of this kind of compounds, the development of new synthetic methods for the efficient preparation of tetrahydroimidazo[1,2-*a*]pyridine motifs is an interesting challenge. Thus we first focused our attention on the optimization of this multi-component reaction.

In the initial experiment, the aza–ene type reaction of 2-(2,4-dichlorophenyl)methyleneimidazolidine **2a** with 4-chlorobenzaldehyde **3a** and malononitrile **4** was chosen as the model reaction for the optimum reaction conditions in different catalysts and solvents, and the results are listed in Table 1. As can be seen from Table 1, there was no reaction without addition of any catalyst at room temperature (Table 1, entry 1), and under reflux temperature only 27% yield was obtained (Table 1, entry 2), while with Et_3N (0.5 equiv) in refluxing CH_3CN for 3 h the yield of **5a** can reach 55% (Table 1, entry 3). So we investigated other bases and found that in the presence of K_2CO_3, KOH, pyridine, piperidine, DABCO or DMAP, the reactions became sluggish and the yields of the corresponding products were lower than with Et_3N (Table 1, entries 4–9). Then, the amount of Et_3N was tested (Table 1, entries 10–13). It was found that, with Et_3N (0.2 equiv) as the catalyst, **5a** could be produced in 80% yield in refluxing MeCN for 3 h (Table 1, entry 11). However, with the increase of the catalytic amount, the yields of **5a** were not further improved. Next, the model reaction was performed in other solvents, such as EtOH, CH_3OH, THF or DMF, the corresponding products were obtained in only 55%, 35%, 38%, and 40% yields, respectively, even if the reaction time was prolonged to 10 h (Table 1, entries 14–17). Thus, it was clear from the experiments that the best conditions for **5a** should be Et_3N (0.2 equiv) as base and MeCN as solvent at 80 °C for 3 h (Table 1, entry 11).

Having established the optimal conditions, we then examined the efficiency of the protocol to other substrates. Three 2-(2-chloroaroyl)methyleneimidazolidines **2a**–**c** were then examined for their reactions with 10 aromatic aldehydes **3a**–**j** and malononitrile **4** under the optimized conditions (Table 2).

Table 1
Optimization of reaction conditions for compound **5a**



Entry	Base (equiv)	Solv.	Temp (°C)	Time (h)	Yield[a] (%)
1	—[b]	MeCN	rt	24	Nil
2	—[b]	MeCN	80	24	27
3	Et_3N (0.5)	MeCN	80	3	55
4	K_2CO_3(0.5)	MeCN	80	10	38
5	KOH (0.5)	MeCN	80	10	35
6	Pyridine (0.5)	MeCN	80	5	37
7	Piperidine (0.5)	MeCN	80	5	40
8	DABCO (0.5)	MeCN	80	5	35
9	DMAP (0.5)	MeCN	80	5	30
10	Et_3N (0.1)	MeCN	80	3	51
11	Et_3N (0.2)	MeCN	80	3	80
12	Et_3N (0.3)	MeCN	80	3	74
13	Et_3N (0.4)	MeCN	80	3	67
14	Et_3N (0.2)	EtOH	78	10	55
15	Et_3N (0.2)	CH_3OH	66	10	35
16	Et_3N (0.2)	THF	66	10	38
17	Et_3N (0.2)	DMF	100	10	40

[a] Isolated yield.
[b] No base.

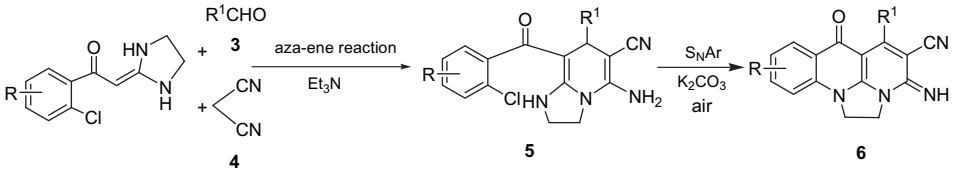
For precursors **3** bearing either electron-donating or electron-withdrawing substituents, the reactions proceeded very smoothly and gave the corresponding products **5a**–**p** in good yields in all cases. This reaction unveils a new reactivity pattern of the precursors **2** with **3** and malononitrile **4**, and provides an efficient route to tetrahydroimidazo[1,2-*a*]pyridines **5**.

The subsequent S_NAr cyclization requires a suitable base to enhance the nucleophilicity of heterocyclic nitrogen atom by deprotonation and capture of the HCl released during the reaction. We directly explored the use of various **5** in the presence of K_2CO_3 in DMF at 100 °C under atmospheric oxygen via cyclization/oxidation step for about 4 h, the solvent being evaporated and then water added, finally the residue being washed with ethanol. To our surprise, the reaction conditions did not require any optimization, and led to the formation of the corresponding tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines **6** in almost quantitative yields (Table 2). Interestingly, workup of the reaction mixture did not afford the expected compounds **6′**, and the isolated products were unexpectedly found to be compounds **6**, which are more stable by aerobic oxidation/dehydrogenation (Scheme 1). In the ^1H NMR spectrum of **6j**, apart from the aromatic protons and four CH_2 protons in imidazole moiety, only one NH is present (δ 7.21, disappeared after addition of D_2O). Compared to **5**, the absence of CH proton (δ 3.8–4.8) in pyridine moiety indicates that 6π electron system exists in **6**.

Aza–ene reaction and nucleophilic substitution are two major reactions in organic chemistry. Encouraged by this successful transformation, we replaced **4** with ethyl 2-cyanoacetate **7** and came to investigate this reaction. 4-Chlorobenzaldehyde **3a** reacted with 2-(2,4-dichlorophenyl)methyleneimidazolidine **2a** and **7** under the same conditions as described above. It is noteworthy that the reaction proceeded without the formation of product **8″a** but an unexpected white solid of **8a** (Scheme 2).

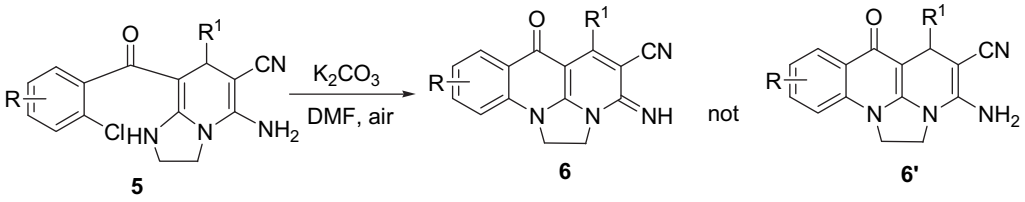
Comparing this aza–ene reaction with our early reported three-component reactions[25a] of β-(2-chloroaroyl)thioacetanilides with

Table 2
The synthesis of compounds **5a**–**p** and **6a**–**p**

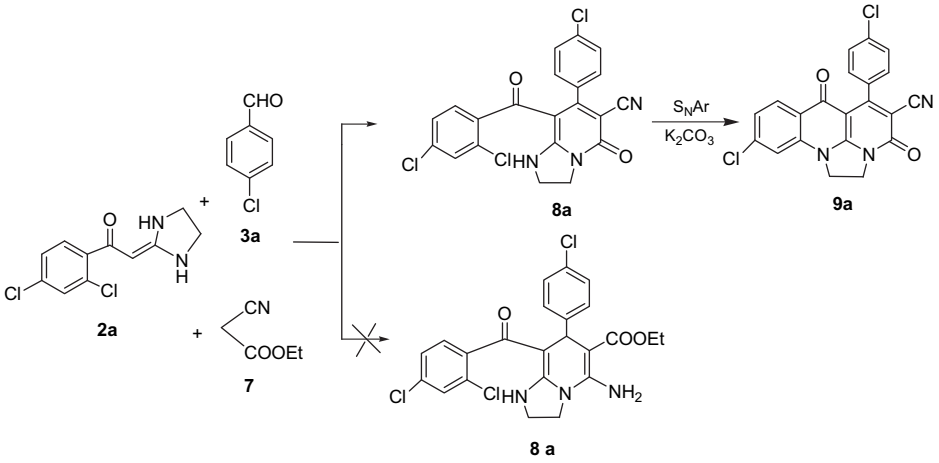


Entry	R	R^1	Time (h)	aza–ene product	Yield[a] (%)	Time (h)	S_NAr-product	Yield[b] (%)
1	4-Cl	4-ClC_6H_4	3	**5a**	80	4	**6a**	98
2	4-Cl	2,4-$Cl_2C_6H_3$	3	**5b**	78	4	**6b**	99
3	4-Cl	4-BrC_6H_4	3	**5c**	76	4	**6c**	98
4	4-Cl	2-BrC_6H_4	3	**5d**	74	4	**6d**	98
5	4-Cl	4-FC_6H_4	3	**5e**	78	4	**6e**	99
6	4-Cl	2-FC_6H_4	3	**5f**	77	4	**6f**	98
7	4-Cl	3-FC_6H_4	3	**5g**	74	4	**6g**	99
8	4-Cl	4-$NO_2C_6H_4$	3	**5h**	82	4	**6h**	98
9	4-Cl	3-$NO_2C_6H_4$	3	**5i**	75	4	**6i**	99
10	4-Cl	C_6H_5	3	**5j**	72	4	**6j**	99
11	4-Cl	4-$CH_3C_6H_4$	3	**5k**	70	4	**6k**	98
12	4-Cl	4-$MeOC_6H_4$	3	**5l**	67	4	**6l**	98
13	4-Cl	3-$CH_3C_6H_4$	3	**5m**	65	4	**6m**	98
14	4-Cl	3-$MeOC_6H_4$	3	**5n**	61	4	**6n**	97
15	4-Cl-5-F	4-ClC_6H_4	3	**5o**	72	4	**6o**	99
16	5-Cl	4-ClC_6H_4	3	**5p**	74	4	**6p**	98

[a] Yield of pure, isolated product based on **2**.
[b] Yield of pure, isolated product based on **5**.



Scheme 1.



Scheme 2.

aromatic aldehydes and ethyl 2-cyanoacetate, it is worth mentioning that there is a big difference in regioselectivity. According to the latter reaction mechanism, the reaction of **2a** with **3a** and **7** would generate the product **8″a**, in which the C(O)OEt group would remain after the intramolecular addition/cyclization of one of NH to cyano carbon atom. But, in our present experiment, **8a** was formed by intramolecular nucleophilic addition of one of NH group in **2a** to carbonyl carbon atom, which was followed by intramolecular S_NAr to obtain corresponding compound **9a** in nearly quantitative conversion (Scheme 2).

The structure of **8a** was conformed by IR in combination with NMR and HRMS spectroscopic data. The IR spectrum of **8a** shows a strong absorption at 2223 cm^{-1} because of the C≡N group. The absence of C(O)OEt absorption at 1740 cm^{-1} confirms that the

cyclization/oxidation of the initially formed aza–ene adduct occurs with participation of ethyoxy carbonyl group resulting in the formation of **8a**. In the ^{1}H NMR spectrum of **8a**, apart from the aromatic protons and four CH_2 protons (δ 3.90–4.19) in imidazole moiety, only one NH is present (δ 9.67, disappeared after addition of D_2O). The ^{13}C NMR spectrum of **8a** shows 20 distinct resonances in agreement with the proposed structure. The HRMS spectrum of **8a** displays a molecular ion peak at the appropriate *m*/*z* value (444.0065 $[M+H]^+$).

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 **9** to be performed in one-pot procedure. We performed aza–ene type reaction of **2a** with 4-chlorobenzaldehyde **3a** and ethyl 2-cyanoacetate **7** by simply combining three components in MeCN and Et_3N as base. Stirring the mixture at 80 °C readily gave the expected aza–ene type adduct **8a**, 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. After completion of the reaction as monitored by TLC, the mixture was added into an amount of ice-water to precipitate the product, which was then collected by filtration, and washed with ethanol to afford the expected product **9a** in total yield of 81%.

Several other aldehydes **3b**–**h** also reacted with **2a** and ethyl 2-cyanoacetate **7** under above conditions via aza–ene reaction, imine–enamine tautomerization, intramolecular cyclization, and oxidation/intramolecular S_NAr to afford corresponding products **9b**–**h** in good yields (Table 3).

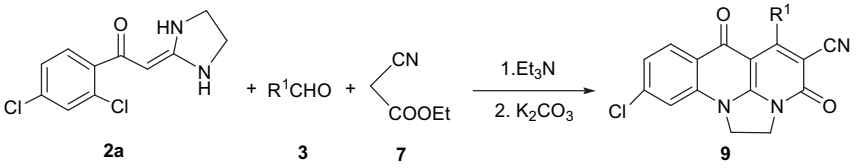
It should be noted that atmospheric oxygen is important for this reaction. In order to gain more insight into the reaction mechanism, we performed the three-component reaction with 2-(2,4-dichlorophenyl)methyleneimidazolidine **2a** with **7** and **3c** under dry N_2. To our delight, the unaromatized intermediate **8′c** was isolated, subsequently treatment of the intermediate in the presence of K_2CO_3 in DMF at 100 °C under atmospheric oxygen gave the corresponding aromatized compound **9c**. The monocrystal structure of **8′c** was unequivocally established by X-ray diffraction analysis (Fig. 2).[28]

The structural determination of all products **9a**–**h** was achieved following their analytical and spectral data and unequivocally confirmed by X-ray diffraction analysis of monocrystal of **9a** (Fig. 3).[28]

It is worthy of noting that all the isolated products only need recrystallization or washing rather than column chromatography. This ease of purification makes this methodology facile, practical, and rapid to execute.

On the basis of the above experimental results together with the related reports, a possible mechanism for the formation of tetrahedroimidazo[1,2-*a*]pyridines and tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines is proposed and depicted in Scheme 3. First, compounds **3** proceed through Knoevenagel condensation with **4** or **7** to give intermediates **A** or **E**. Then, the heterocyclic ketene aminal **2**, acted as hetero-ene components due to the strong nucleophilicity at the α-position of the ketene *N*,*N*-acetals, reacts with **A** or **E** to form the intermediates **B** or **F**,[16] which undergo a rapid imine–enamine tautomerization to give **C** or **G**. Next, intramolecular cyclization of **C** or **G** lead to the formation of fused

Table 3
Synthesis of **9a**–**h**



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

Entry	R^1	Time (h)	S_NAr-product	Yield[a] (%)
1	4-ClC_6H_4	4	**9a**	81
2	2,4-$Cl_2C_6H_3$	4	**9b**	79
3	4-BrC_6H_4	4	**9c**	76
4	2-BrC_6H_4	4	**9d**	72
5	4-FC_6H_4	4	**9e**	83
6	3-FC_6H_4	4	**9f**	79
7	C_6H_5	4	**9g**	74
8	4-$MeOC_6H_4$	4	**9h**	67

[a] Total isolated yield.

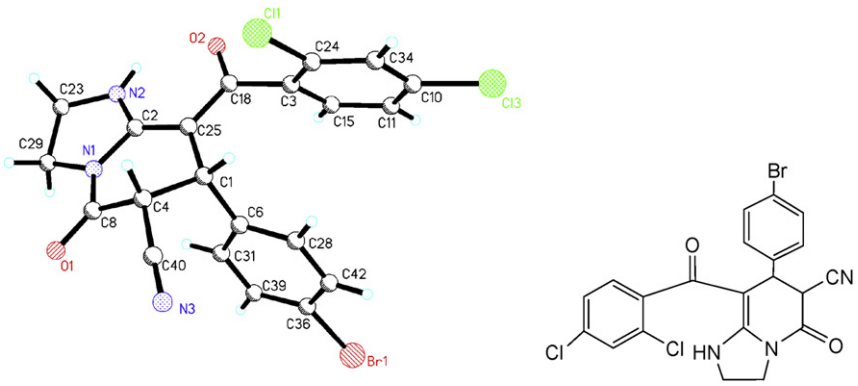


Fig. 2. The X-ray crystal structure of **8′c**.

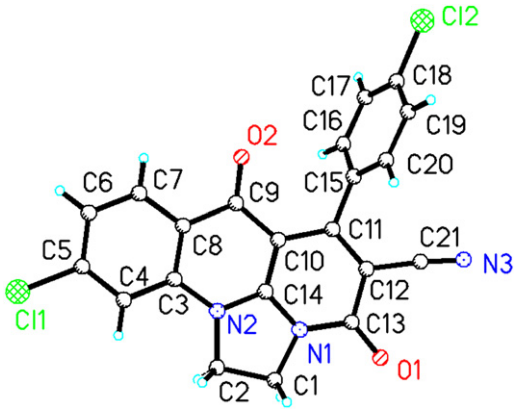
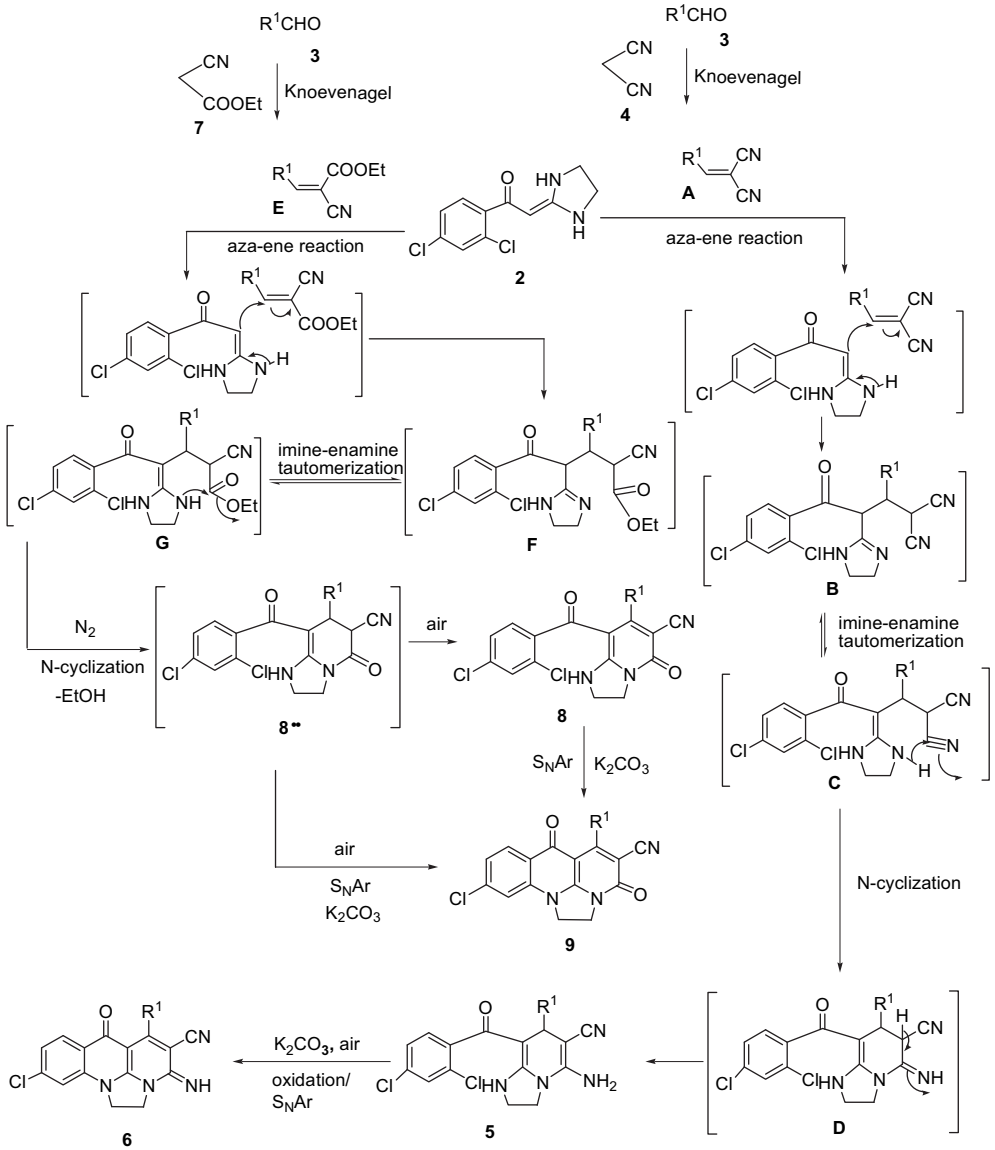


Fig. 3. The X-ray crystal structure of **9a**.

heterocyclic imidazo[1,2-*a*]pyridine motifs **5** or **8**. Finally, an intramolecular nucleophilic aryl substitution of the *o*-chloro of aryl group (S_NAr) by attack of NH group leads to new and highly functionalized **6** or **9**[29] with elimination of HCl.

3. Conclusion

In summary, we have successfully demonstrated the application of 2-(2-chloroaroyl)methyleneimidazolidines **2** to synthesize tetrahydroimidazo[1,2-*a*]pyridines and tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines. These studies highlighted the concept of a substrate-design to the development of novel multicomponent reactions by simply incorporating an *ortho*-halo group into the aryl ring of 2-benzoylmethyleneimidazolidine as new synthons, which show structural features of highly polarized push–pull interaction C=C double bond and Cl atom as leaving group subjecting to intramolecular S_NAr. Undoubtedly, this domino synthetic strategy presented provides a convenient and general way to construct the target molecules from readily available starting materials under mild conditions. A possible mechanism involved in the ring closure cascade reaction including Knoevenagel condensation, aza–ene reaction, intramolecular imine–enamine tautomerization, followed by cyclocondensation, oxidation and intramolecular S_NAr was proposed. In this domino reaction, nine different active sites are involved, two C–C bonds, two C–N bonds, and two new rings are constructed in the chemical transformation. Further



Scheme 3. Plausible mechanism for the formation of benzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines **6** and **9**.

investigations to expand the scope of the diversity oriented synthesis of 2-(2-chloroaroyl)methyleneimidazolidines as versatile building blocks by the combined use of domino and MCRs are in progress and will be reported elsewhere in due course.

4. Experimental section

4.1. General

All the reagents were purchased from local suppliers and used without purification. The starting materials **2** were prepared following the published literature procedure.[30] Chromatography refers to open column chromatography on silica gel (100–200 mesh).

Melting points were recorded on a RY-1 microscopic melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on 500 MHz and ^{13}C NMR spectra were recorded on 125 MHz in DMSO-d_6 or acetone-d_6 by using a Bruker Avance 500 spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS or solvent as internal standards. IR spectra were recorded on a Nicolet 510P FT-IR spectrometer and only major peaks are reported in cm^{-1}. Mass spectra were performed on an Ultima Global spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on SMART APEX II instrument.

4.2. General procedure for the preparation of products 5a–p and 6a–p

A solution of 2-(2-chloroaroyl)methyleneimidazolidines **2** (2.0 mmol), aldehydes **3** (2.4 mmol), and malononitrile **4** (2.4 mmol) was refluxed for a certain period of time in dry MeCN (20 mL) containing Et_3N (0.4 mmol, 0.2 equiv). After completion of the reaction as indicated by TLC (petroleum ether–EtOAc, 2:1, v/v), the solvent was removed under vacuum and the residue was recrystallized from EtOAc to afford the products **5**. A mixture of corresponding **5** (1.0 mmol) and K_2CO_3 (1 mmol) was heated to 100 °C in DMF (15 mL). After completion of the reaction as indicated by TLC (petroleum ether–EtOAc, 2:3, v/v), the mixture was cooled to room temperature. An amount of ice-water was added to precipitate the product, which was then filtered and washed with ethanol to give the pure products **6**.

*4.2.1. 5-Amino-7-(4-chlorophenyl)-8-(2,4-dichlorobenzoyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5a**).* Yellow powder; mp 297–299 °C; IR (KBr, cm^{-1}): 3469, 3265, 2180, 1660, 1634, 1443, 1377, 1298; δ_H (DMSO-d_6) 3.79–3.95 (m, 5H, 2×CH$_2$, CH), 6.25–7.60 (m, 9H, ArH, NH$_2$), 9.45 (s, 1H, NH); δ_C (DMSO-d_6) 43.5, 44.3, 59.9, 87.6, 122.4, 127.8, 128.7, 129.0, 129.1, 129.2, 129.7, 131.3, 133.9, 140.4, 147.7, 150.4, 156.0, 187.2; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{16}Cl_3N_4O$, 445.0390; found, 445.0383.

*4.2.2. 10-Chloro-6-(4-chlorophenyl)-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6a**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3204, 2212, 1627, 1595, 1563, 1540, 1470; δ_H (DMSO-d_6) 4.30 (t, J=9.0 Hz, 2H, CH$_2$), 4.53 (t, J=9.0 Hz, 2H, CH$_2$), 7.28–7.89 (m, 8H, NH, ArH); δ_C (DMSO-d_6) 45.2, 45.9, 97.6, 115.7, 116.1, 123.3, 124.3, 128.4, 129.0, 129.9, 133.8, 135.7, 138.2, 138.5, 151.5, 156.3, 171.5; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{13}Cl_2N_4O$, 407.0466; found, 407.0459.

*4.2.3. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(2,4-dichlorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5b**).* Yellow powder; mp 231–233 °C; IR (KBr, cm^{-1}): 3450, 3222, 2177, 1659, 1585, 1447, 1375, 1296; δ_H (DMSO-d_6) 3.80–4.62 (m, 5H, 2×CH$_2$, CH), 6.14–7.57 (m, 8H, ArH, NH$_2$), 9.46 (s, 1H, NH); δ_C (DMSO-d_6) 43.4, 44.1, 57.7, 87.2, 121.5, 127.5, 128.1, 129.5, 129.9, 131.4, 132.0, 132.6, 133.6, 140.2, 145.2, 150.6, 155.9, 186.8; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{15}Cl_4N_4O$, 479.0000; found, 478.9995.

*4.2.4. 10-Chloro-6-(2,4-dichlorophenyl)-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6b**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3292, 2216, 1629, 1594, 1564, 1538, 1470; δ_H (DMSO-d_6) 4.36 (t, J=9.5 Hz, 2H, CH$_2$), 4.57 (t, J=9.0 Hz, 2H, CH$_2$), 7.36–7.92 (m, 7H, NH, ArH); δ_C (DMSO-d_6) 45.5, 46.2, 98.2, 115.7, 122.8, 124.4, 127.9, 129.0, 130.7, 132.6, 134.5, 135.1, 138.5, 150.9, 151.4, 157.1, 158.3, 171.3; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{12}Cl_3N_4O$, 441.0077; found, 441.0085.

*4.2.5. 5-Amino-7-(4-bromophenyl)-8-(2,4-dichlorobenzoyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5c**).* Yellow powder; mp 278–280 °C; IR (KBr, cm^{-1}): 3463, 3264, 2180, 1660, 1634, 1442, 1375, 1297; δ_H (DMSO-d_6) 3.78–3.94 (m, 5H, 2×CH$_2$, CH), 6.25–7.73 (m, 9H, ArH, NH$_2$), 9.45 (s, 1H, NH); δ_C (DMSO-d_6) 43.3, 44.1, 59.4, 87.1, 119.3, 122.0, 127.4, 129.1, 129.8, 131.2, 132.3, 133.4, 140.2, 140.1, 148.0, 150.2, 155.7, 186.7; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{16}BrCl_2N_4O$, 488.9885; found, 488.9875.

*4.2.6. 6-(4-Bromophenyl)-10-chloro-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6c**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3300, 2213, 1628, 1595, 1566, 1538, 1469; δ_H (DMSO-d_6) 4.34 (t, J=8.5 Hz, 2H, CH$_2$), 4.57 (t, J=8.5 Hz, 2H, CH$_2$), 7.25–7.95 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 45.8, 46.4, 98.1, 98.4, 116.1, 116.5, 122.9, 123.6, 124.7, 129.4, 130.5, 131.7, 136.5, 138.7, 138.9, 151.8, 152.1, 156.5, 171.9; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{13}BrClN_4O$, 450.9961; found, 450.9971.

*4.2.7. 5-Amino-7-(2-bromophenyl)-8-(2,4-dichlorobenzoyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5d**).* Yellow powder; mp 147–149 °C; IR (KBr, cm^{-1}): 3426, 3327, 2171, 1654, 1636, 1520, 1450, 1371, 1293; δ_H (DMSO-d_6) 3.79–4.62 (m, 5H, 2×CH$_2$, CH), 5.98–7.56 (m, 9H, ArH, NH$_2$), 9.48 (s, 1H, NH); δ_C (DMSO-d_6) 43.6, 44.3, 58.7, 88.1, 121.7, 123.0, 127.6, 128.5, 128.8, 129.4, 129.6, 130.3, 132.4, 133.7, 140.6, 148.0, 150.8, 156.1, 187.1; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{16}BrCl_2N_4O$, 488.9885; found, 488.9883.

*4.2.8. 6-(2-Bromophenyl)-10-chloro-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6d**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3298, 2216, 1627, 1595, 1564, 1536, 1470; δ_H (DMSO-d_6) 4.32 (m, 2H, CH$_2$), 4.53 (m, 2H, CH$_2$), 7.21–7.86 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 45.6, 46.3, 98.5, 115.9, 116.0, 121.4, 123.3, 124.6, 128.4, 129.3, 129.4, 130.9, 132.8, 138.5, 138.8, 151.3, 151.4, 156.1, 171.4; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{13}BrClN_4O$, 450.9961; found, 450.9954.

*4.2.9. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(4-fluorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5e**).* Yellow powder; mp 222–224 °C; IR (KBr, cm^{-1}): 3474, 3264, 2179, 1661, 1635, 1506, 1444, 1375, 1296 ; δ_H (DMSO-d_6) 3.78–4.30 (m, 5H, 2×CH$_2$, CH), 6.23–7.62 (m, 9H, ArH, NH$_2$), 9.43 (s, 1H, NH); δ_C (DMSO-d_6) 43.3, 44.0, 59.8, 87.5, 114.9, 115.1, 122.1, 127.3, 128.6, 129.5, 130.1, 133.3, 140.3, 145.4, 150.0, 155.6, 160.0, 161.9, 186.8; HRMS (ESI-TOF, [M+H]$^+$): calcd for $C_{21}H_{16}Cl_2FN_4O$, 429.0685; found, 429.0665.

*4.2.10. 10-Chloro-6-(4-fluorophenyl)-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6e**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3296, 2218, 1623, 1594, 1564, 1539, 1469 ; δ_H (acetone-d_6) 4.50 (t, J=8.5 Hz, 2H, CH$_2$), 4.76 (t, J=8.50 Hz, 2H, CH$_2$), 7.14–7.98 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 43.3, 44.0, 87.5, 114.9, 115.1, 122.1, 127.3, 128.7, 133.4, 139.6, 140.0,

145.2, 145.9, 150.0, 155.7, 160.0, 161.9, 186.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}ClFN_4O$, 391.0762; found, 391.0756.

*4.2.11. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(2-fluorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5f**).* Yellow powder; mp 149–151 °C; IR (KBr, cm^{-1}): 3471, 3294, 2177, 1657, 1587, 1509, 1445, 1373, 1296; δ_H (DMSO-d_6) 3.79–4.40 (m, 5H, 2×CH_2, CH), 6.12–7.60 (m, 9H, ArH, NH_2), 9.44 (s, 1H, NH); δ_C (DMSO-d_6) 33.8, 43.6, 44.3, 58.3, 87.1, 115.3, 122.2, 124.9, 127.6, 128.6, 129.0, 129.9, 132.6, 133.6, 135.5, 136.4, 139.8, 140.3, 150.8, 156.1, 159.2, 161.0, 186.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{16}N_4OFCl_2$, 429.0685; found, 429.0680.

*4.2.12. 10-Chloro-6-(2-fluorophenyl)-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8] naphthyridine-5-carbonitrile (**6f**).* Yellow powder; decompose, >250 °C; IR (KBr, cm^{-1}): 3290, 2212, 1659, 1597, 1560, 1539, 1470; δ_H (DMSO-d_6) 4.32 (t, J=8.5 Hz, 2H, CH_2), 4.53 (t, J=8.5 Hz, 2H, CH_2), 6.85–7.93 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 45.1, 45.7, 98.5, 115.4, 115.6, 118.9, 123.0, 124.0, 124.3, 124.6, 128.7, 129.0, 129.9, 130.5, 131.4, 138.3, 138.5, 151.5, 154.4, 156.4, 158.1, 171.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}N_4OFCl$, 391.0762; found, 391.0753.

*4.2.13. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(3-fluorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5g**).* Yellow powder; mp 207–209 °C; IR (KBr, cm^{-1}): 3421, 3267, 2179, 1659, 1447, 1371, 1295; δ_H (DMSO-d_6) 3.79–3.94 (m, 5H, 2×CH_2, CH), 6.24–7.65 (m, 9H, ArH, NH_2), 9.43 (s, 1H, NH); δ_C (DMSO-d_6) 43.4, 44.1, 59.2, 87.2, 113.3, 115.1, 118.6, 122.1, 123.1, 127.4, 129.1, 130.1, 133.4, 140.4, 150.3, 152.3, 155.7, 161.5, 163.4, 186.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{16}Cl_2FN_4O$, 429.0685; found, 429.0673.

*4.2.14. 10-Chloro-6-(3-fluorophenyl)-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6g**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3311, 2214, 1630, 1595, 1564, 1533, 1469; δ_H (DMSO-d_6) 4.32 (t, J=8.5 Hz, 2H, CH_2), 4.55 (t, J=8.5 Hz, 2H, CH_2), 7.08–7.92 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 45.5, 46.0, 98.1, 114.9, 115.1, 115.7, 123.3, 124.1, 124.4, 129.2, 130.6, 138.2, 138.7, 139.3, 145.2, 149.4, 152.1, 152.5, 156.0, 161.2, 171.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}ClFN_4O$, 391.0762; found, 391.0762.

*4.2.15. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(4-nitrophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5h**).* Yellow powder; mp 283–286 °C; IR (KBr, cm^{-1}): 3460, 2923, 2178, 1660, 1636, 1515, 1446, 1346, 1298; δ_H (DMSO-d_6) 3.80–4.04 (m, 5H, 2×CH_2, CH), 6.48 (s, 2H, NH_2), 6.88–7.99 (m, 7H, ArH), 9.51 (s, 1H, NH); δ_C (DMSO-d_6) 41.5, 43.5, 44.1, 58.6, 86.7, 121.7, 123.9, 127.6, 128.2, 129.2, 133.7, 139.9, 146.3, 150.5, 155.8, 186.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{16}Cl_2N_5O_3$, 456.0630; found, 456.0634.

*4.2.16. 10-Chloro-benzo-1,2-dihydroimidazo[3,2,1-ij][1,8]naphthyridine-4-imino-5-carbonitrile-6-(4-nitrophenyl)-7-one (**6h**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3439, 2216, 1622, 1595, 1563, 1541, 1472, 1345; δ_H (DMSO-d_6) 4.32 (t, J=9.0 Hz, 2H, CH_2), 4.58 (t, J=9.0 Hz, 2H, CH_2), 7.34–8.32 (m, 8H, ArH, NH); δ_C (TFA-d) 49.1, 50.5, 94.5, 106.7, 113.4, 127.0, 130.6, 131.0, 132.5, 139.9, 142.7, 147.5, 151.5, 151.8, 156.1, 166.4, 177.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}ClN_5O_3$, 418.0707; found, 418.0690.

*4.2.17. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(3-nitrophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5i**).* Yellow powder; mp 223–225 °C; IR (KBr, cm^{-1}): 3447, 2176, 1660, 1636, 1526, 1448, 1349, 1297; δ_H (DMSO-d_6) 3.80–4.27 (m, 5H, 2×CH_2, CH), 6.48 (s, 2H, NH_2), 6.48–7.91 (m, 7H, ArH), 9.52 (d, 1H, NH); δ_C (DMSO-d_6) 40.6, 41.5, 43.4, 44.1, 58.6, 86.9, 121.6, 121.8, 127.5, 129.2, 130.2, 133.7, 139.7, 147.7, 150.4, 155.7, 186.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{16}Cl_2N_5O_3$, 456.0630; found, 456.0627.

*4.2.18. 10-Chloro-benzo-1,2-dihydroimidazo[3,2,1-ij][1,8]naphthyridine-4-imino-5-carbonitrile-6-(3-nitrophenyl)-7-one (**6i**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3440, 2211, 1628, 1597, 1565, 1541, 1472, 1348; δ_H (TFA-d) 5.86–5.95 (m, 4H, 2×CH_2), 8.33–9.32 (m, 8H, ArH, NH); δ_C (TFA-d) 49.1, 50.3, 95.0, 106.7, 125.0, 125.4, 128.5, 130.7, 132.5, 133.4, 136.2, 137.2, 139.9, 147.6, 150.9, 151.6, 156.2, 166.1, 178.0; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}ClN_5O_3$, 418.0707; found, 418.0708.

*4.2.19. 5-Amino-8-(2,4-dichlorobenzoyl)-7-phenyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5j**).* Yellow powder; mp 245–247 °C; IR (KBr, cm^{-1}): 3436, 3348, 2177, 1657, 1446, 1373, 1295; δ_H (DMSO-d_6) 3.79–3.97 (m, 5H, 2×CH_2, CH), 6.15–7.60 (m, 10H, ArH, NH_2), 9.43 (s, 1H, NH); δ_C (DMSO-d_6) 41.2, 43.3, 44.1, 59.9, 87.6, 122.2, 126.4, 126.9, 127.2, 128.4, 129.2, 129.8, 130.2, 133.3, 140.2, 148.7, 150.1, 155.8, 186.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{17}Cl_2N_4O$, 411.0779; found, 411.0768.

*4.2.20. 10-Chloro-4-imino-7-oxo-6-phenyl-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6j**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3296, 2216, 1628, 1595, 1564, 1537, 1471; δ_H (acetone-d_6) 4.55 (t, J=8.5 Hz, 2H, CH_2), 4.81 (t, J=8.5 Hz, 2H, CH_2), 7.21 (s, 1H, NH), 7.32–8.02 (m, 8H, ArH); δ_C (DMSO-d_6) 45.4, 46.0, 98.1, 115.6, 116.3, 123.4, 124.2, 127.8, 128.3, 128.9, 129.2, 136.8, 138.3, 138.5, 151.2, 152.0, 157.4, 171.5; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{14}ClN_4O$, 373.0856; found, 373.0852.

*4.2.21. 5-Amino-8-(2,4-dichlorobenzoyl)-7-p-tolyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5k**).* Yellow powder; mp 203–205 °C; IR (KBr, cm^{-1}): 3473, 3263, 2184, 1662, 1633, 1441, 1376, 1298; δ_H (DMSO-d_6) 2.20 (s, 3H, CH_3), 3.78–3.94 (m, 5H, 2×CH_2, CH), 6.27–7.70 (m, 9H, ArH, NH_2), 9.40 (s, 1H, NH); δ_C (DMSO-d_6) 21.1, 43.3, 44.1, 60.2, 87.7, 114.2, 122.2, 126.8, 127.3, 128.3, 128.9, 133.3, 135.3, 140.2, 145.5, 150.1, 155.8, 186.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{19}Cl_2N_4O$, 425.0936; found, 425.0938.

*4.2.22. 10-Chloro-4-imino-7-oxo-6-(p-tolyl)-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6k**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3305, 2209, 1670,1645, 1622, 1595, 1562, 1539, 1472 ; δ_H (DMSO-d_6) 2.40 (s, 3H, CH_3), 4.34 (t, J=8.5 Hz, 2H, CH_2), 4.56 (t, J=8.5 Hz, 2H, CH_2), 7.17–7.92 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 21.5, 45.4, 46.1, 98.1, 115.6, 116.4, 116.8, 123.4, 124.4, 127.9, 128.8, 129.1, 133.9, 138.7, 139.5, 148.4, 151.5, 152.2, 197.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{16}ClN_4O$, 387.1013; found, 387.1021.

*4.2.23. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(4-methoxyphenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5l**).* Yellow powder; mp 274–276 °C; IR (KBr, cm^{-1}): 3433, 3206, 2179, 1664, 1636, 1443, 1378, 1299; δ_H (DMSO-d_6) 3.67 (s, 3H, OCH_3), 3.78–3.94 (m, 5H, 2×CH_2, CH), 6.26 (s, 2H, NH_2), 6.52–7.60 (m, 7H, ArH), 9.39 (s, 1H, NH); δ_C (DMSO-d_6) 43.3, 44.0, 55.4, 60.3, 87.8, 113.8, 122.3, 127.3, 127.8, 127.9, 128.8, 128.9, 129.5, 133.2, 140.3, 149.9, 155.7, 157.9, 186.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{19}Cl_2N_4O_2$, 441.0885; found, 441.0879.

*4.2.24. 10-Chloro-4-imino-6-(4-methoxyphenyl)-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8] naphthyridine-5-carbonitrile (**6l**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3256, 2217, 1667, 1632, 1593, 1564, 1539, 1468; δ_H (DMSO-d_6) 3.84 (s, 3H, OCH_3), 4.31–4.37 (m, 2H, CH_2), 4.53–4.57 (m, 2H, CH_2), 6.99–7.94 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 45.2, 45.9, 55.6, 97.8, 113.5, 115.5, 116.6, 123.5, 124.4, 125.9,

129.1, 129.7, 131.7, 137.5, 138.4, 143.0, 148.2, 160.2, 171.5; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{16}N_4O_2Cl$, 403.0962; found, 403.0957.

*4.2.25. 5-Amino-8-(2,4-dichlorobenzoyl)-7-m-tolyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5m**).* Yellow powder; mp 155–157 °C; IR (KBr, cm^{-1}): 3327, 2178, 1654, 1636, 1586, 1448, 1374, 1295; δ_H (DMSO-d_6) 2.12 (s, 3H, CH_3), 3.76–3.97 (m, 5H, 2×CH_2, CH), 6.20–7.20 (m, 9H, ArH, NH_2), 9.42 (s, 1H, NH); δ_C (DMSO-d_6) 21.5, 41.4, 43.3, 44.1, 60.1, 87.9, 122.2, 124.4, 127.0, 127.2, 127.6, 128.4, 133.3, 137.0, 150.1, 155.7, 186.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{19}Cl_2N_4O$, 425.0936; found, 425.0935.

*4.2.26. 10-Chloro-benzo-1,2-dihydroimidazo[3,2,1-ij][1,8]naphthyridine-4-imino-5-carbonitrile-6-m-tolyl-7-one (**6m**).* Yellow powder; mp>300 °C; IR (KBr, cm^{-1}): 3447, 2214, 1625, 1593, 1562, 1538, 1471, 1348; δ_H (TFA-*d*) 3.13 (s, 3H, CH_3), 5.77–5.85 (m, 4H, 2×CH_2), 7.89–8.99 (m, 7H, ArH,); δ_C (TFA-*d*) 22.2, 48.9, 50.1, 94.8, 106.8, 116.0, 125.3, 126.4, 129.7, 130.3, 131.7, 132.6, 135.0, 135.3, 139.8, 142.7, 147.2, 151.5, 156.0, 170.3, 178.2; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{16}ClN_4O$, 387.1013; found, 387.1020.

*4.2.27. 5-Amino-8-(2,4-dichlorobenzoyl)-7-(3-methoxyphenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5n**).* Yellow powder; mp 200–202 °C; IR (KBr, cm^{-1}): 3439, 2177, 1656, 1586, 1446, 1371, 1295; δ_H (DMSO-d_6) 3.57 (s, 3H, OCH_3), 3.75–3.94 (m, 4H, 2×CH_2), 4.68 (s, 1H, CH), 5.99–7.50 (m, 9H, ArH, NH_2), 9.40 (s, 1H, NH); δ_C (DMSO-d_6) 41.4, 43.3, 44.1, 55.2, 59.9, 87.7, 111.7, 112.7, 119.4, 122.1, 127.3, 127.5, 129.4, 129.6, 133.4, 150.2, 155.8, 159.3, 186.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{19}Cl_2N_4O_2$, 441.0885; found, 441.0888.

*4.2.28. 10-Chloro-benzo-1,2-dihydroimidazo[3,2,1-ij][1,8]naphthyridine-4-imino-5-carbonitrile-6-(3-methoxyphenyl)-7-one (**6n**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3442, 2215, 1626, 1595, 1562, 1539, 1471, 1345; δ_H (TFA-*d*) 4.73 (s, 3H, OCH_3), 5.77–5.82 (m, 4H, 2×CH_2), 7.78–9.00 (m, 7H, ArH,); δ_C (TFA-*d*) 49.6, 50.7, 58.9, 95.6, 107.6, 116.8, 119.1, 119.8, 123.7, 126.0, 131.2, 133.3, 134.4, 137.7, 140.6, 148.0, 152.3, 156.8, 162.4, 169.7, 178.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{16}ClN_4O_2$, 403.0962; found, 403.0957.

*4.2.29. 5-Amino-7-(4-chlorophenyl)-8-(2,4-dichloro-5-fluorobenzoyl)-1,2,3,7-tetrahydro-imidazo[1,2-a]pyridine-6-carbonitrile (**5o**).* Yellow powder; mp 254–256 °C; IR (KBr, cm^{-1}): 3407, 3338, 2177, 1660, 1634, 1509, 1485, 1448, 1396, 1294; δ_H (DMSO-d_6) 3.79 (t, *J*=9.5 Hz, 2H, CH_2), 3.87–3.96 (m, 3H, CH_2, CH), 6.36 (s, 2H, NH_2), 6.68–7.79 (m, 6H, ArH), 9.46 (s, 1H, NH); δ_C (DMSO-d_6) 43.4, 44.1, 59.8, 87.0, 120.2, 120.3, 121.9, 124.5, 117.0, 128.3, 128.8, 130.9, 147.2, 142.6, 149.9, 155.3, 155.9, 157.2, 185.0 ; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{15}Cl_3N_4OF$, 463.0295; found, 463.0276.

*4.2.30. 10-Chloro-6-(4-chlorophenyl)-9-fluoro-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8] naphthyridine-5-carbonitrile (**6o**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3322, 2221, 1668, 1629, 1581, 1536, 1471, 1377, 1240; δ_H (acetone-d_6) 4.19–4.32 (m, 4H, 2×CH_2), 6.98–7.35 (m, 7H, ArH, NH); δ_C (acetone-d_6) 43.3, 44.6, 97.7, 115.8, 117.2, 117.4, 125.8, 127.3, 127.9, 130.4, 130.7, 134.6, 135.3, 141.2, 152.2, 154.7, 156.5, 156.8, 157.9, 186.4; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{12}Cl_2FN_4O$, 425.0372; found, 425.0358.

*4.2.31. 5-Amino-7-(4-chlorophenyl)-8-(2,5-dichlorobenzoyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**5p**).* Yellow powder; mp 230–232 °C; IR (KBr, cm^{-1}): 3470, 3246, 2179, 1667, 1634, 1440, 1377, 1295; δ_H (DMSO-d_6) 3.92–4.08 (m, 5H, 2×CH_2, CH), 7.01–7.15 (m, 9H, NH_2, ArH), 9.72 (s, 1H, NH); δ_C (DMSO-d_6) 43.6, 43.9, 44.7, 90.8, 98.0, 117.1, 128.2, 128.5, 129.5, 129.7, 131.1, 134.1, 135.5, 142.4, 151.4, 157.1, 187.2; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{16}Cl_3N_4O$, 445.0390; found, 445.0393.

*4.2.32. 9-Chloro-6-(4-chlorophenyl)-4-imino-7-oxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**6p**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 3214, 2216, 1654, 1623, 1596, 1563, 1540, 1471; δ_H (acetone-d_6) 4.56 (t, *J*=9.0 Hz, 2H, CH_2), 4.82 (t, *J*=9.0 Hz, 2H, CH_2), 7.27–7.99 (m, 8H, ArH, NH); δ_C (DMSO-d_6) 45.5, 46.0, 97.9, 116.2, 118.3, 125.9, 126.2, 128.5, 128.8, 129.9, 133.6, 133.9, 135.7, 136.1, 149.3, 151.2, 151.8, 156.1, 171.1; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}Cl_2N_4O$, 407.0466; found, 407.0478.

4.3. General procedure for synthesis of products 9a–h

A solution of 2-(2-chloroaroyl)methyleneimidazolidines **2** (2.0 mmol), aldehydes **3** (2.4 mmol), and ethyl 2-cyanoacetate **7** (2.4 mmol) was refluxed for a certain period of time in dry MeCN (20 mL) containing Et_3N (0.4 mmol, 0.2 equiv). After completion of the reaction as indicated by TLC (petroleum ether–EtOAc, 2:1, v/v), the solvent was removed under vacuum, the residue was mixed with 1 equiv of K_2CO_3 in DMF, and the mixture was heated to 100 °C. After completion of the reaction as monitored by TLC (petroleum ether–EtOAc, 2:3, v/v), the mixture was added into an amount of ice-water to precipitate the product, which was then collected by filtration and washed with ethanol to afford the expected products **9**.

*4.3.1. 10-Chloro-6-(4-chlorophenyl)-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9a**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2222, 1670, 1645, 1602, 1563, 1539, 790; δ_H (DMSO-d_6) 4.47–4.51 (m, 2H, CH_2), 4.61–4.65 (m, 2H, CH_2), 7.35–7.99 (m, 7H, ArH); δ_C (DMSO-d_6) 45.2, 46.6, 99.5, 100.5, 116.1, 116.4, 123.5, 125.1, 128.9, 129.7, 130.2, 134.5, 135.5, 138.5, 139.6, 151.3, 157.9, 160.8, 172.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{12}Cl_2N_3O_2$, 408.0307; found, 408.0309.

*4.3.2. 10-Chloro-6-(2,4-dichlorophenyl)-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9b**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2219, 1672, 1644, 1608, 1564, 1540, 1467; δ_H (DMSO-d_6) 4.50–4.54 (m, 2H, CH_2), 4.62–4.66 (m, 2H, CH_2), 7.37–8.00 (m, 6H, ArH); δ_C (DMSO-d_6) 45.2, 46.7, 99.4, 100.6, 115.4, 116.5, 123.0, 123.2, 125.1, 128.3, 129.4, 130.8, 132.5, 135.0, 138.5, 139.6, 151.1, 157.6, 157.7, 172.5; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{11}Cl_3N_3O_2$, 441.9917; found, 441.9928.

*4.3.3. 6-(4-Bromophenyl)-10-chloro-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9c**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2224, 1644, 1602, 1566, 1542, 1463; δ_H (DMSO-d_6) 4.47–4.51 (m, 2H, CH_2), 4.61–4.65 (m, 2H, CH_2), 7.28–7.99 (m, 7H, ArH); δ_C (DMSO-d_6) 45.0, 46.5, 99.1, 100.2, 115.7, 116.3, 122.8, 123.4, 124.9, 129.4, 130.1, 131.7, 135.6, 138.4, 139.3, 151.1, 157.6, 160.5, 172.5; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{12}BrClN_3O_2$, 451.9801; found, 451.9803.

*4.3.4. 6-(2-Bromophenyl)-10-chloro-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9d**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2221, 1655, 1610, 1567, 1541, 1460; δ_H (DMSO-d_6) 4.48–4.55 (m, 2H, CH_2), 4.62–4.66 (m, 2H, CH_2), 7.28–7.98 (m, 7H, ArH); δ_C (DMSO-d_6) 45.1, 46.5, 99.1, 100.4, 115.2, 116.2, 120.8, 122.9, 124.9, 128.3, 129.0, 129.3, 130.9, 132.6, 137.8, 138.3, 139.3, 150.9, 157.6, 160.0, 172.1; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{12}BrClN_3O_2$, 451.9801; found, 451.9819.

*4.3.5. 10-Chloro-6-(4-fluorophenyl)-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9e**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2224, 1679, 1646,

1599, 1565, 1541, 1515, 1471, 791; δ_H (DMSO-d_6) 4.46–4.51 (m, 2H, CH_2), 4.60–4.64 (m, 2H, CH_2), 7.30–8.00 (m, 7H, ArH); δ_C (DMSO-d_6) 45.1, 46.5, 99.6, 100.5, 115.6, 115.8, 116.1, 116.3, 123.4, 124.9, 129.6, 130.6, 132.7, 138.4, 139.4, 151.2, 157.8, 161.0, 172.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{12}ClFN_3O_2$, 392.0602; found, 392.0621.

*4.3.6. 10-Chloro-6-(3-fluorophenyl)-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9f**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2225, 1684, 1648, 1606, 1599, 1564, 1540, 1471, 790, 760; δ_H (DMSO-d_6) 4.41–4.45 (m, 2H, CH_2), 4.54–4.58 (m, 2H, CH_2), 6.80–7.95 (m, 7H, ArH); δ_C (DMSO-d_6) 45.2, 46.6, 99.8, 100.7, 115.8, 115.9, 116.0, 116.2, 116.4, 123.1, 124.3, 124.4, 125.0, 129.5, 130.1, 132.0, 132.1, 138.4, 139.5, 151.1, 155.7, 157.8, 158.1, 160.1, 172.6; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{12}ClFN_3O_2$, 392.0602; found, 392.0607.

*4.3.7. 10-Chloro-4,7-dioxo-6-phenyl-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9g**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2224, 1644, 1602, 1566, 1542, 1463; δ_H (DMSO-d_6) 4.47–4.50 (m, 2H, CH_2), 4.60–4.63 (m, 2H, CH_2), 7.31–7.99 (m, 8H, ArH); δ_C (DMSO-d_6) 44.8, 46.2, 99.2, 100.3, 115.9, 116.0, 123.2, 124.7, 127.8, 128.4, 129.3, 129.4, 136.3, 138.2, 139.1, 151.0, 157.7, 161.8, 172.4; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}ClN_3O_2$, 374.0696; found, 374.0695.

*4.3.8. 10-Chloro-6-(4-methoxyphenyl)-4,7-dioxo-1,2,4,7-tetrahydrobenzo[b]imidazo[1,2,3-ij][1,8]naphthyridine-5-carbonitrile (**9h**).* Yellow powder; mp >300 °C; IR (KBr, cm^{-1}): 2219, 1645, 1605, 1566, 1543, 1462; δ_H (DMSO-d_6) 3.84 (s, 3H, CH_3), 4.44–4.48 (m, 2H, CH_2), 4.58–4.62 (m, 2H, CH_2), 7.01–7.99 (m, 7H, ArH); δ_C (DMSO-d_6) 44.9, 46.2, 55.9, 99.3, 100.5, 113.9, 116.2, 116.4, 123.6, 124.9, 128.3, 129.6, 130.0, 138.4, 139.3, 151.2, 158.0, 160.6, 161.9, 172.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{15}ClN_3O_3$, 404.0802; found, 404.0798.

*4.3.9. 7-(4-Chlorophenyl)-8-(2,4-dichlorobenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**8a**).* Yellow powder; mp 262–264 °C; IR (KBr, cm^{-1}): 3291, 2223, 1661, 1612, 1574, 1533, 1494, 1470, 1322, 1293, 824, 787; δ_H (DMSO-d_6) 3.90–3.94 (m, 2H, CH_2), 4.15–4.19 (m, 2H, CH_2), 7.07–7.23 (m, 7H, ArH), 9.67 (s, 1H, NH); δ_C (DMSO-d_6) 44.2, 44.3, 91.5, 100.9, 117.1, 127.4, 128.6, 129.4, 130.8, 131.5, 131.7, 134.8, 135.2, 135.3, 139.6, 157.4, 158.6, 161.4, 189.6; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{13}Cl_3N_3O_2$, 444.0073; found, 444.0065.

*4.3.10. 7-(4-Bromophenyl)-8-(2,4-dichlorobenzoyl)-5-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carbonitrile (**8′c**).* White powder, mp 265–266 °C; IR (KBr, cm^{-1}): 3295, 2260, 1709, 1645, 1588, 1556, 1534, 1488, 1451, 822, 747; δ_H (DMSO-d_6) 3.73–3.97 (m, 5H, 2×CH_2, CH), 4.96 (d, J=5.0 Hz, 1H, CH), 6.74–7.60 (m, 7H, ArH), 9.65 (s, 1H, NH); δ_C (DMSO-d_6) 41.2, 42.0, 42.8, 43.8, 87.3, 115.8, 121.2, 127.5, 128.9, 129.2, 129.4, 129.9, 130.1, 131.8, 133.8, 139.5, 155.2, 161.1, 186.2; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{15}BrCl_2N_3O_2$, 489.9725; found, 489.9739.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.049. These data include MOL files and InChIKeys of the most important compounds described in this article.

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28. Crystallographic data for **8′c** and **9a** have been deposited in the Cambridge Crystallographic Data Centre with the deposition numbers CCDC 761670 and 733858, respectively. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44 (0)1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).
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