Facile three-component domino reactions for the synthesis of 2-arylimidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines

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Facile three-component domino reactions for the synthesis of 2-arylimidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines

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Abstract: The three-component domino reactions of pyridine/isoquinoline, phenacyl bromide and substituted (*E*)-*N*-hydroxyarylimidoyl chloride in the presence of triethylamine afforded a series of 2-arylimidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines. This one pot three-component transformation presumably proceeds *via* ylide generation/annulation/fragmentation/dehydration domino sequence of reactions.

Keywords: multi-component; domino; pyridine/isoquinoline; phenacyl bromide; (*E*)-*N*-hydroxyarylimidoyl chloride; 2-arylimidazo[1,2-*a*]pyridines; 2-arylimidazo[2,1-*a*]isoquinolines.

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Imidazo[1,2-*a*]pyridines are biologically and pharmaceutically active heterocycles, which have received considerable attention in the field of pharmaceutical industry owing to their broad range of useful activities such as antibacterial,[1] antifungal,[2] antiviral,[3] antiulcer,[4] and anti-inflammatory.[5] They have also been characterized as selective cyclin-dependent kinase inhibitors,[6] calcium channel blockers,[7] β-amyloid formation inhibitors,[8] and benzodiazepine receptor agonists.[9] They also act as orally active nonpeptide bradykinin B2 receptor antagonists,[10] besides being prevalent as the core structure of several drug formulations such as alpidem, zolpidem, olprinone, zolimidine and minodronic acid, which are available currently in the market (Figure 1).

Imidazo[1,2-*a*]pyridines have been synthesized by the two-component reactions of: (i) 2-aminopyridines with α-haloketones,[11] α-diazoketones,[12] 1-phenylethanol,[13] alkynyl-(phenyl)iodonium salts,[14] γ-bromodypnone,[15] 2-chloroacetaldehyde[16] and acetophenones[17] and (ii) 2-amino-1-[*R*-benzotriazol-1-ylmethyl]pyridinium chlorides with aldehydes in the presence of DBU in dimethylformamide.[18] Most of the three-component syntheses of these compounds include the reaction of 2-aminopyridines with (i) benzyl halides and isocyanides in the presence of potassium carbonate in dimethyl sulfoxide,[19] (ii) aldehydes and isocyanides in the presence of $ZnCl_2$ in dioxane under thermal or microwave irradiation[20] and (iii) aldehydes and phenylacetylene in the presence of *p*-TSA with $CuSO_4$ in toluene.[21] Other approaches involve the reactions of (i) *N*-fluoropyridinium triflate, isonitriles and nitrile in the presence of $NaBH(OAc)_3$[22] and (ii) pyridines, phenacyl bromides and thiocyanates in the presence of potassium carbonate in toluene.[23] This class of compounds has also been prepared in three steps.[24]

These methods often involve harsh reaction conditions, inconsistent yields and long reaction time. Under this context, we report a simple method that has emerged serendipitously, for the preparation of these compounds. For some time, we have been interested in the synthesis of novel heterocycles employing (i) the reaction of pyridinium ylides and (ii) 1,3-dipolar cycloaddition reactions of 1,3-dipoles such as nitrile oxides/azomethine ylides with α,β-unsaturated carbonyl systems. In this context, we were prompted to investigate whether the pyridinium ylides and nitrile oxides, both being 1,3-dipoles, could react among themselves to furnish novel hybrid heterocycles, *viz.* functionalized dihydropyrido[1,2-*e*][1,2,5]oxadiazines (Scheme 1) by forming bonds between oppositely charged nuclei. Interestingly, the reaction (*E*)-*N*-hydroxyarylimidoyl chloride,

phenacyl bromide and pyridine/isoquinoline in the presence of triethylamine in acetonitrile afforded imidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines through three-component domino reactions in a one pot operation.

We started our study with the optimization of the model three-component reaction between pyridine (1 mmol), phenacyl bromide (1 mmol) and (*E*)-4-chloro-*N*-hydroxybenzimidoyl chloride (1 mmol) in the presence of potassium carbonate (1 mmol) in acetonitrile at 80 °C for 4 h, which afforded 3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine **5b** in 83% yield (Table 1, entry 8). When triethylamine was used instead of potassium carbonate in this reaction in acetonitrile at 80 °C for 3 h, an excellent yield of 96% of **5b** was obtained (Table 1, entry 1). As the selection of an appropriate reaction medium is crucial for the success of reactions, the three-component reaction under heating was examined in *N*,*N*-dimethylformamide, methanol, ethanol, dioxane, water and solvent-free condition (entries 2–7). From the data listed in Table 1, acetonitrile has emerged as the solvent of choice furnishing the highest yield of the product.

The model reaction was also investigated employing different bases, *viz*. sodium acetate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane and L-proline (entries 9–12, Table 1). The reaction in presence of KOH or NaOH failed to afford any characterizable product. Presumably, the nitrile oxides, generated initially from the reaction of (*E*)-4-chloro-*N*-hydroxybenzimidoyl chloride by dehydrohalogenation, underwent decomposition in presence of these bases. From the above results, triethylamine-acetonitrile pair is discerned as the ideal choice of base and solvent for the synthesis of **5b** in excellent yield. After identifying these optimal conditions, the scope of this transformation was examined further (Scheme 2 and Table 2**)** employing pyridine/isoquinoline (1 mmol), phenacyl bromide (1 mmol) and a series of substituted (*E*)-*N*-hydroxyarylimidoyl chlorides (1 mmol) in the presence of triethylamine in acetonitrile at 80 °C for 3-4 h. After completion of the reaction, the solvent was removed and the residue purified by column chromatography to obtain a series of novel 2-arylimidazo[1,2-*a*]pyridines **5** and 2-arylimidazo[2,1-*a*]isoquinolines **6** in 85-96% yields[25] (Table 2). It is pertinent to note that this transformation occurred successfully in the presence of both strongly electron-releasing (4-MeO) as well as electron-withdrawing substituents (4-CF_3 and 4-NO_2) in the aryl ring of (*E*)-*N*-hydroxyarylimidoyl chlorides.

The structure of the products **5** and **6** was deduced from one- and two-dimensional NMR spectroscopic data as detailed for **5b** as a representative example (Figure 2). In the ^{1}H NMR spectrum of **5b,** H-3 of imidazole ring appears as a singlet at 7.85 ppm, which shows HMBCs with C-2 and C-8a at 144.8 and 145.8 ppm respectively. The H-5 appears as a doublet of triplets at 8.13 ppm (J = 6.9 and 1.2 Hz), which shows HMBCs with C-3, C-6 and C-8a at 108.1, 112.5 and 145.8 ppm respectively. Similarly, the H-6 gives a triplet of doublets at 6.80 ppm (J = 6.3 and 1.2 Hz), which shows HMBCs with C-8 at 117.6 ppm. The J value of 1.2 Hz found for H-3 and H-6 presumably arises from long range W-coupling. The H-7 gives a triplet of doublets at 7.19 ppm (J = 7.8 and 1.2 Hz) and shows HMBCs with C-8a and C-5 at 145.8 and 125.6 ppm respectively, while H-8 appearing as a multiplet at 7.61-7.64 ppm shows HMBC with C-6 at 112.5 ppm. Finally, the X-ray crystallographic study[26] of a single crystal of **6d** confirmed the structure of **6 (**Figure 3**)**.

A plausible mechanism for the formation of 2-arylimidazo[1,2-*a*]pyridines **5** and isoquinolines **6** is depicted in Scheme 3. Presumably, this transformation is triggered by the formation of pyridinium salt **7** from the reaction of pyridine **1** and phenacyl bromide **3**, which reacts with base to furnish ylide **8**. This ylide intermediate **8** then reacts with nitrile oxide **9** (generated *in situ* from the dehydrochlorination of **4** upon reaction with triethylamine) to afford the intermediate **10**, which subsequently undergoes annulation giving intermediate **11**. Then intermediate **11** undergoes base-catalyzed fragmentation with concomitant protonation leading to the intermediate **12**, which finally affords the product **5/6** via dehydration. To our knowledge, this synthesis of 2-arylimidazo[1,2-*a*]pyridines **5** and 2-arylimidazo[2,1-*a*]isoquinolines **6** through the three-component protocol is reported for the first time.

In conclusion, we have described a facile three-component synthesis of novel 2-arylimidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines *via* domino sequence of reactions from simple, readily available starting materials in a one pot operation.

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SP thanks the Department of Science and Technology, New Delhi for a major research project (SR/S1/OC-50/2011) and for funds under IRHPA program for the purchase of a high resolution NMR spectrometer. PG thanks the Council of Scientific and Industrial Research, New Delhi for the award of Senior Research Fellowship.

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25. General procedure for the synthesis of 2-arylimidazo[1,2-*a*]pyridines **5** and 2-arylimidazo[2,1-*a*]isoquinolines **6**: A mixture of pyridine/isoquinoline (1 mmol), phenacyl bromide (1 mmol) and (*E*)-*N*-hydroxyarylimidoyl chloride (1 mmol) in CH_3CN (10 ml) in the presence of triethylamine (1 mmol) was heated at 80 °C for 3-4 h. The reaction progress was monitored by thin layer chromatography. After completion of the reaction, the solvent was removed and the product was purified by flash column using petroleum ether–ethyl acetate mixture (4:1 v/v) as eluent to afford pure 2-arylimidazo[1,2-*a*]pyridines **5** and 2-arylimidazo[2,1-*a*]isoquinolines **6**. Characterization data for representative compounds **5b** and **6h** are given below.

2-(4-Chlorophenyl)imidazo[1,2-a]pyridine **5b**: Isolated as white solid. Yield: 96%; mp = 208– 209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.80 (td, *J* = 6.3, 1.2 Hz, 1H), 7.19 (td, *J* = 7.8, 1.2 Hz, 1H), 7.40-7.42 (m, 2H), 7.61– 7.64 (m, 1H), 7.85 (s, 1H), 7.88– 7.91 (m, 2H), 8.13 (dt, *J* = 6.9, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 108.1, 112.5, 117.6, 124.8, 125.6, 127.3, 128.9, 132.4, 133.7, 144.8, 145.8; Anal. Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25 %. Found C, 68.37; H, 3.89; N, 12.36 %.

2-p-Tolylimidazo[2,1-a]isoquinoline **6h:** Isolated as white solid. Yield: 89%; mp = 153– 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.39 (s, 3H), 6.98 (d, *J* = 7.2 Hz, 1H), 7.24– 7.23 (m, 2H), 7.52– 7.57 (m, 1H), 7.60– 7.68 (m, 2H), 7.75 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 8.71– 8.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 21.1, 109.4, 112.6, 122.7,

123.2, 123.5, 125.6, 126.7, 127.8, 129.2, 131.1, 137.0, 142.9, 143.8; Anal. Calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84 %. Found C, 83.78; H, 5.57; N, 10.73 %.

26. Crystallographic data (excluding structure factors) for compound **6d** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 930324. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].

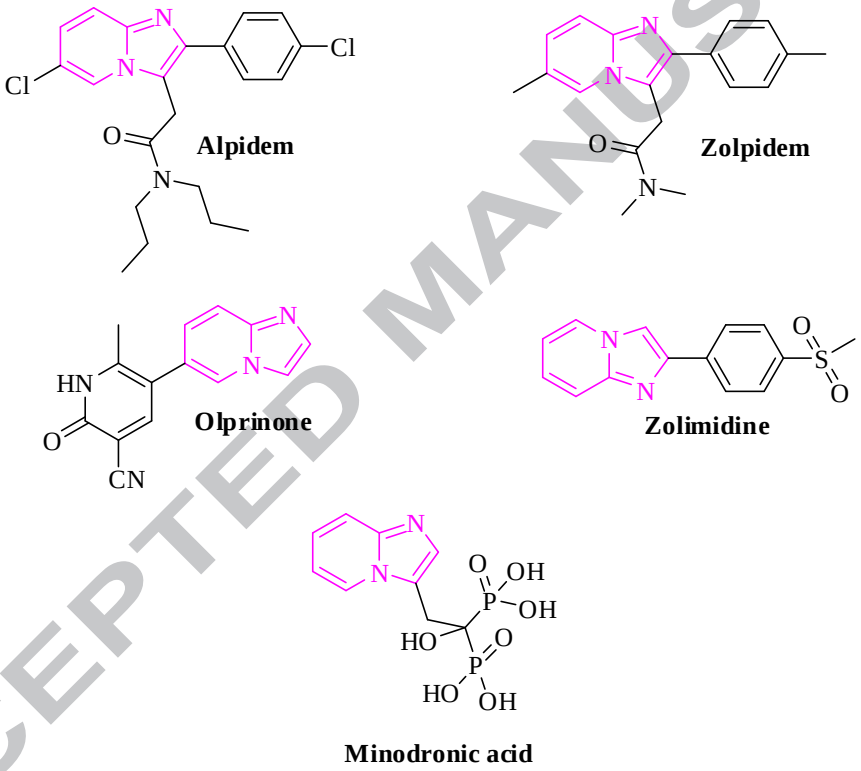
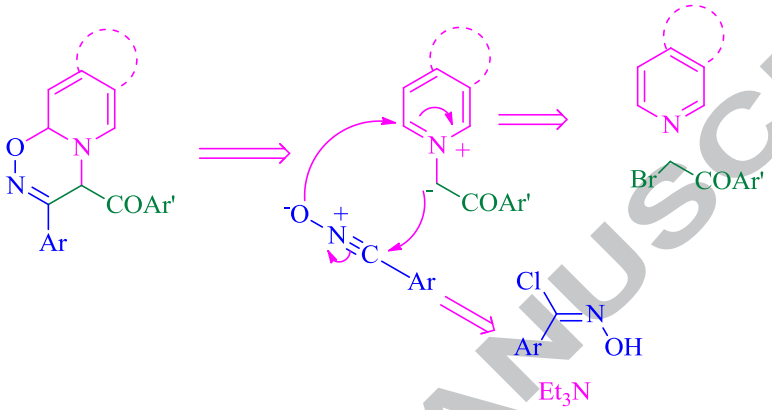
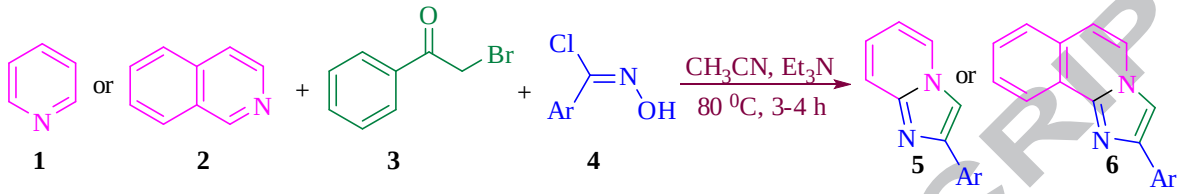


Figure 1. Structures of some imidazo[1,2-*a*]pyridine drug molecules.



Scheme 1. Retrosynthesis of dihydropyrido[1,2-*e*][1,2,5]oxadiazines



Scheme 2. Three-component synthesis of 2-arylimidazo[1,2-*a*]pyridines **5** and 2-arylimidazo[2,1-*a*]isoquinolines **6**.

Table 1. Solvent- and base-screen for the synthesis of **5b**

Entry	Base	Solvent	Reaction time (h)	Yield of 5b[a] (%)
1	Et_3N	CH_3CN	3	96
2	Et_3N	DMF	7	61
3	Et_3N	MeOH	5	69
4	Et_3N	EtOH	5	77
5	Et_3N	Dioxane	5	81
6	Et_3N	Water	6	-[b]
7	Et_3N	None	3	45
8	K_2CO_3	CH_3CN	4	83
9	NaOAc	CH_3CN	5	71
10	DBU	CH_3CN	7	67
11	DABCO	CH_3CN	7	61
12	$_L$-Proline	CH_3CN	7	-[b]
13	NaOH	MeOH	10	-[b]
\14	KOH	MeOH	10	-[b]

[a]Isolated yield after purification by column chromatography.
[b]No reaction occurred.

Table 2. Synthesis of 2-arylimidazo[1,2-*a*]pyridines **5** and 2-arylimidazo[2,1-*a*]isoquinolines **6**

Entry	Comp.	Ar	Time (h)	Yield of 5/6 (%)[a]
1	**5a**	C_6H_5	3	91
2	**5b**	4-ClC_6H_4	3	96
3	**5c**	4-$MeOC_6H_4$	4	88
4	**6a**	C_6H_5	3	90
5	**6b**	2-ClC_6H_4	3	92
6	**6c**	4-ClC_6H_4	3	94
7	**6d**	3-FC_6H_4	3	93
8	**6e**	4-FC_6H_4	3	95
9	**6f**	3-BrC_6H_4	4	90
10	**6g**	4-BrC_6H_4	4	91
11	**6h**	4-$NO_2C_6H_4$	3	95
12	**6i**	4-$CF_3C_6H_4$	3	93
13	**6j**	4-$H_3CC_6H_4$	4	89
14	**6k**	4-$MeOC_6H_4$	4	87
15	**6l**	4-$Pr^iC_6H_4$	4	85
16	**6m**	2,4-$Cl_2C_6H_3$	3	92

[a]Isolated yield after purification by column chromatography.

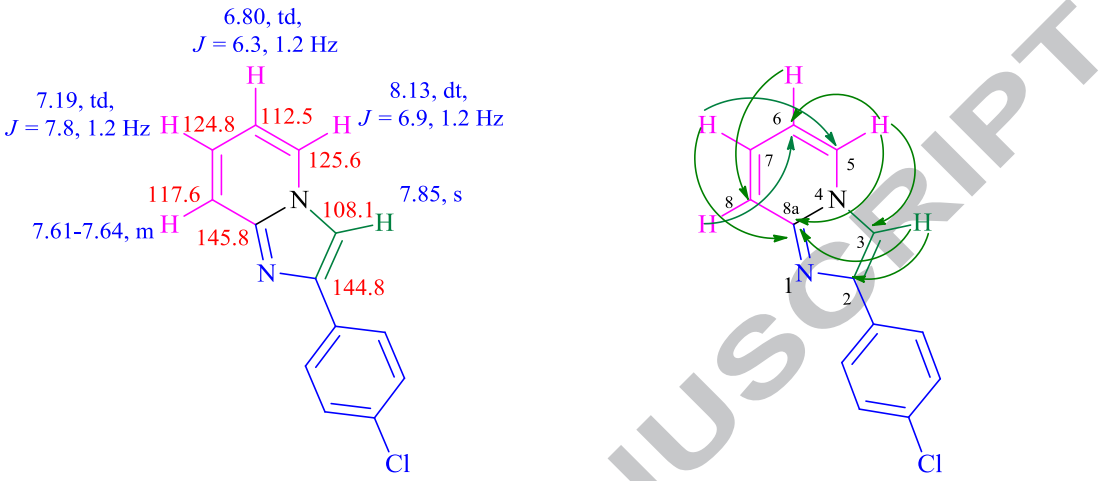


Figure 2. Selected ^{1}H and ^{13}C chemical shifts and HMB correlations of **5b**.

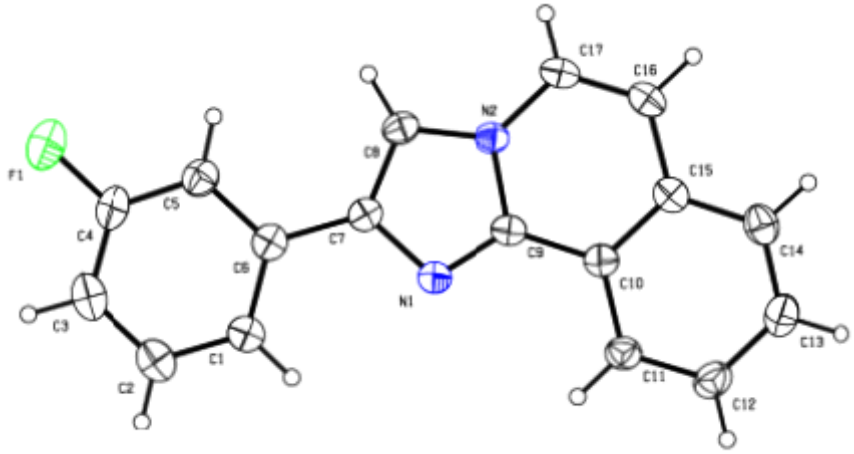
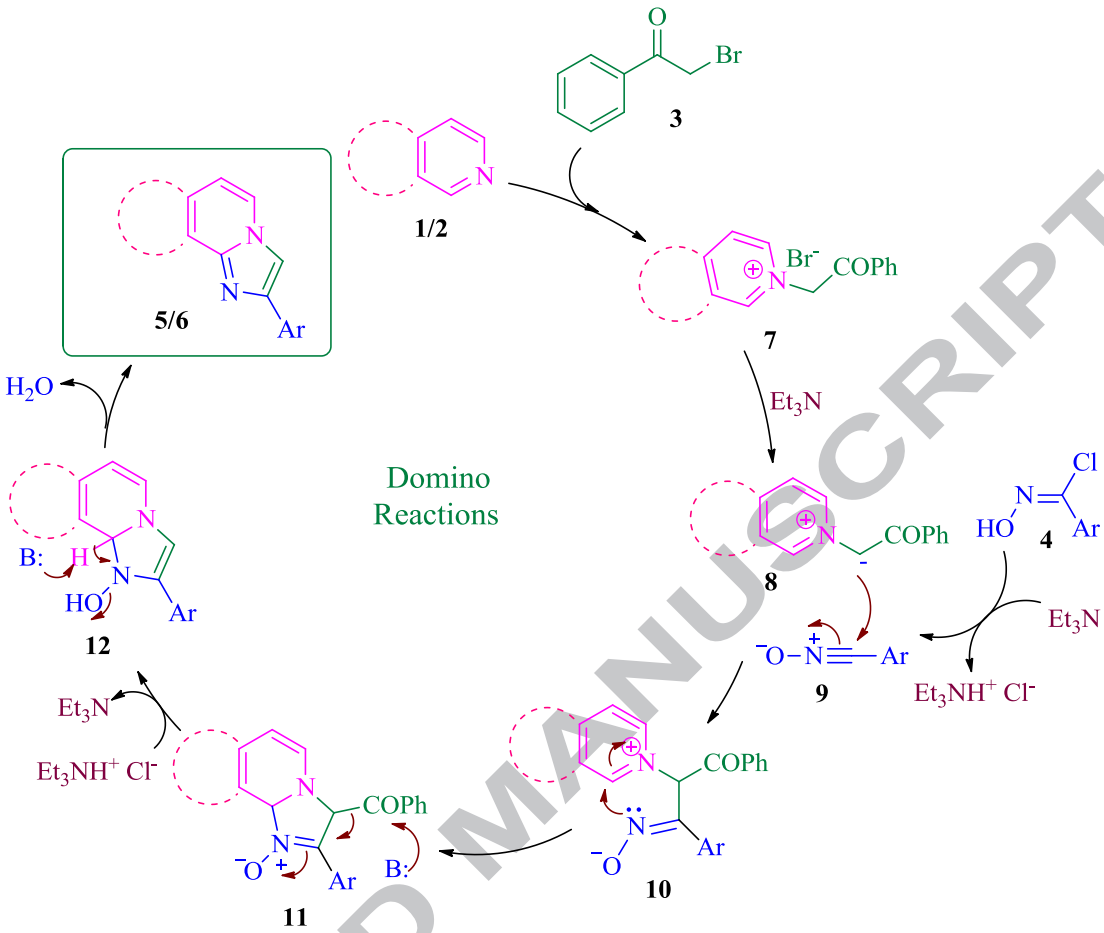


Figure 3. ORTEP diagram for **6d**.



Scheme 3. Probable domino sequence leading to the formation of **5** and **6**.

Graphical Abstract

Facile three-component domino reactions for the synthesis of 2-arylimidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines

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