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Graphical abstract:

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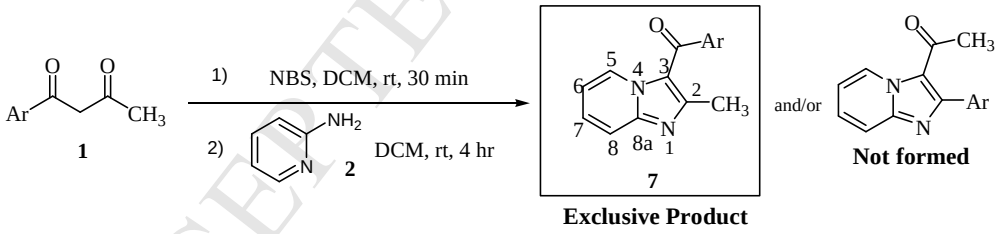

1, 7	a	b	c	d	e	f	g
Ar	Ph	*p*-CH_3Ph	*p*-OCH_3Ph	*p*-FPh	*p*-ClPh	*p*-BrPh	2-thienyl

NBS mediated one-pot regioselective synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines and their unambiguous characterization through 2D NMR and X-ray crystallography

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Abstract:

A simple and mild protocol towards the regioselective synthesis of 1-aryl/heteroaryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones has been developed by one-pot condensation of 2-aminopyridine with 1,3-diketones involving the intermediacy of 2-bromo-1,3-diketones formed *in situ* from 1,3-diketones using N-bromosuccinimide (NBS) in DCM by stirring at room temperature. The structure of the regioisomer has been confirmed unambiguously by the rigorous multinuclear NMR [(^{1}H-^{13}C) HMBC, (^{1}H-^{13}C) HMQC, (^{1}H-^{15}N) HMBC] spectroscopy and X-ray crystallographic studies.

Keywords: 1-Aryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones, regioselective synthesis, 2-aminopyridine, 1,3-diketones, N-bromosuccinimide, 2D-NMR spectroscopy, X-ray crystallography.

Introduction:

Heterocycles are ubiquitous scaffolds in pharmaceuticals and biologically active compounds[1]. Thus development of new and simple methodologies to prepare these useful heterocyclic frameworks has attracted great attention from organic chemists. In recent years, *in situ* generation of one of the reactants, from the simple precursors to condense with another reactant within the reaction vessel in one-pot reaction is a popular synthetic strategy. One-pot method is more economic and convenient in terms of avoidance of intermediates isolation, separation of side products at each step (if not interfering) and higher reaction yields.

Among the fused bicyclic heterocyclic compounds with a heteroatom at the bridgehead position, imidazo[1,2-*a*]pyridine ring system in particular constitutes a privileged substructure and is present in a large number of compounds with remarkable biological activities. Imidazo[1,2-*a*]pyridines have been

reported as anticancer agents by acting as a potent and selective class of cyclin-dependent kinase inhibitors[2], anticoccidial agents[3], benzodiazepine receptors ligands[4], antiviral agents[5], antiprotozoal[6], antiherpes[7] and antitubercular agents[8]. Moreover, imidazo[1,2-*a*]pyridine derivatives have been found in many clinically accepted drugs like Zolpidem (**I**)[9], Alpidem (**II**)[10], Olprinone (**III**)[11] etc (**Figure-1**).

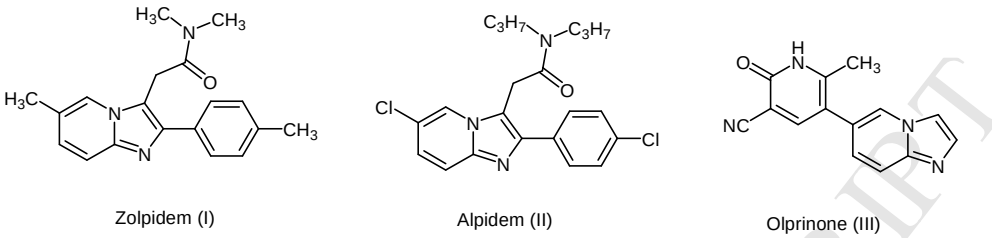
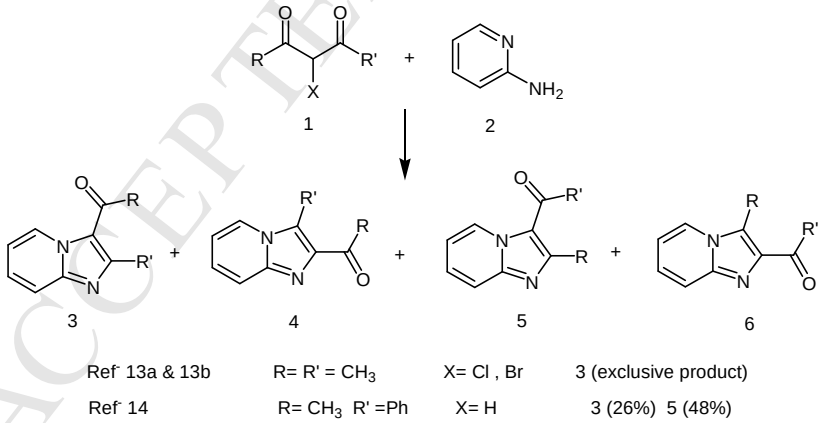


Figure-1 Clinically accepted derivatives of imidazo[1,2-*a*]pyridine

There are several reports cited in the literature for the synthesis of 3-substituted imidazo[1,2-*a*]pyridines dealing with the cyclocondensation of binucleophilic 2-aminopyridine with *α*-functionalized carbonyl compounds e.g. *α*-halo or *α*-tosyloxyketones functioning as bielectrophile[12]. In contrast, there are only a few reports that describe the reaction of 2-aminopyridine with a potential trielectrophile i.e. 2-functionalized diketones despite of the clear opportunity to introduce an acyl group on the imidazo[1,2-*a*]pyridine ring which will act as an additional handle for chemical diversity. Moreover, a reaction of a binucleophile (**2**) with a trielectrophilic entity (**1**), in principle, may produce positional isomers viz two (**3** & **4**) in case of symmetrical 1,3-diketones and four (**3**, **4**, **5** & **6**) in non-symmetrical 1,3-diketones, that are difficult to differentiate (**Scheme-1**).



Scheme-1 Possible positional isomers

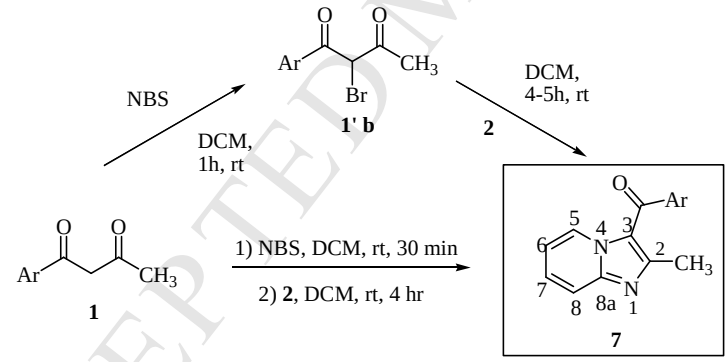
In 2003 and 2004, Anderson group[13a] and Byth et al[13b] both reported, separately the synthesis of 3-acetyl-2-methylimidazo[1,2-*a*]pyridine (**3**) starting from 3-bromo/3-chloropentane-2,4-dione as a symmetrical trielectrophile. In 2011, Wang *et al* reported the formation of two regioisomers, 1-methyl-1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone isomer **3** (**26%**) and 1-phenyl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone **5** (**48%**) by the reaction of 1-phenylbutane-1,3-dione (**1a**) with 2-

aminopyridine (**2**) in presence of diacetoxyiodobenzene and boron trifluoride etherate at 7^{o}C on overnight stirring[14]. Neither of the reports considered the possibility of formation of other possible regioisomers (**4** and **6**), also no specific data for structure assignment was supplied in the support of the proposed regioisomer(s).

In view of these observations and in continuation of our ongoing interest in 2D NMR spectroscopy for characterization of regioisomers[15], we report here an efficient regioselective method for the synthesis of 2,3-differently substituted imidazo[1,2-*a*]pyridines by *in situ* functionalization of non-symmetrical 1,3-diketones by N-bromosuccinimide (NBS) and their subsequent condensation with 2-aminopyridine and characterize the regioisomer(s) on the basis of 2D NMR spectroscopy and X-ray crystallography.

Results and Discussion:

We initially investigated the reaction system with 2-aminopyridine (**2**), 1-phenylbutane-1,3-dione (**1a**) and NBS in DCM at room temperature to determine the optimum conditions for regioselective cyclocondensation (**Scheme-2**). NBS was chosen as *in situ* brominating agent over other reagents e.g. molecular bromine and its complexes[16], tetraalkylammonium tribromide[17]and HBr-H_2O_2[18] due to ease of application, less hazardous nature, better selectivity and low price.



1, 7	a	b	c	d	e	f	g
Ar	Ph	*p*-CH_3Ph	*p*-OCH_3Ph	*p*-FPh	*p*-ClPh	*p*-BrPh	2-thienyl

Scheme-2 Regioselective synthesis of title compound

TLC of the reaction mixture was carried out at regular intervals which indicated that the reaction was complete within 4 hr. resulting in the formation of a single regioisomer, one out of four possible isomers **3**, **4**, **5** & **6** (**Scheme-1**). Moreover, LCMS data of crude sample also ascertained the formation of single isomer. The mass spectrum of the reaction product showed a molecular ion peak m/z 237(100%). The ^{1}H NMR spectrum of **7a** revealed a sharp singlet at δ 2.51 ppm integrating for the three protons assigned to methyl group and peculiar pattern of pyrimidine and the phenyl protons. ^{13}C NMR spectrum also showed the required number of signals thus confirming the successful condensation of two reactants.

Intermediacy of 2-bromo-1,3-diketone has been established by isolation and characterization of them through ^{1}H NMR in one case 2-bromo-1-(4-methylphenyl)butane-1,3-dione (**1'b**). Subsequent reaction of **1'b** with **2** afforded again the same single isomer but the reaction took longer reaction time and yield was much lower as compared to one-pot method.

With the optimized condition in hand, the scope of the methodology was investigated in the reaction with 2-aminopyridine (**2**) and various 1-aryl-1,3-diketones (**1b-f**) and 1-(2-thienyl)-1,3-diketone (**1g**) under similar conditions. A range of electron donating & electron withdrawing substituents at the aryl ring of 1,3-diketones provided reaction products in high yields and excellent regioselectivity even when the reaction was extended to gram scale.

After accomplishing the regioselective synthesis of imidazo[1,2-*a*]pyridines, the next challenge was to assign correct regioisomeric structure to the reaction product out of four. Wang et al. reported formation of two regioisomers 1-methyl-1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (**3**) and 1-phenyl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (**5**) on the basis of ^{1}H and ^{13}C NMR spectroscopy[14]. In the compounds **3** and **5** the methyl protons have been reported as singlet at δ 2.19 and 2.13 ppm, respectively in ^{1}H NMR. These values are very close and may be interchangeable. In ^{13}C NMR, methyl group has been reported at δ 29.8 and δ17.4 and carbonyl carbon at δ189.1 and 186.8 ppm in the compounds **3** and **5**, respectively. These values can also be attributed to the methyl group and carbonyl carbon in other positional isomers **4** and **6** as well (**Scheme-1**).

So, it seems to be unreasonable to draw a conclusion about the structure on the basis of this elementary data. Moreover, in the present study, we observed the signals for methyl protons resonating at δ 2.51 and carbonyl at δ 186.1 ppm which did not match with any of the reported compounds. Therefore, it was envisaged to carry out unambiguous assignments of all ^{1}H, ^{13}C and ^{15}N NMR by 2D NMR [(^{1}H-^{13}C) HMBC, (^{1}H-^{13}C) HMQC, (^{1}H-^{15}N) HMBC] experiments to provide a concluding evidence to support the structure of the reaction product as 1-aryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones (7).

The 2D NMR correlation results has been obtained for compounds **7c**, **7f** and **7g** and their ^{1}H, ^{13}C and ^{15}N chemical shifts has been shown in **Figure-2**.

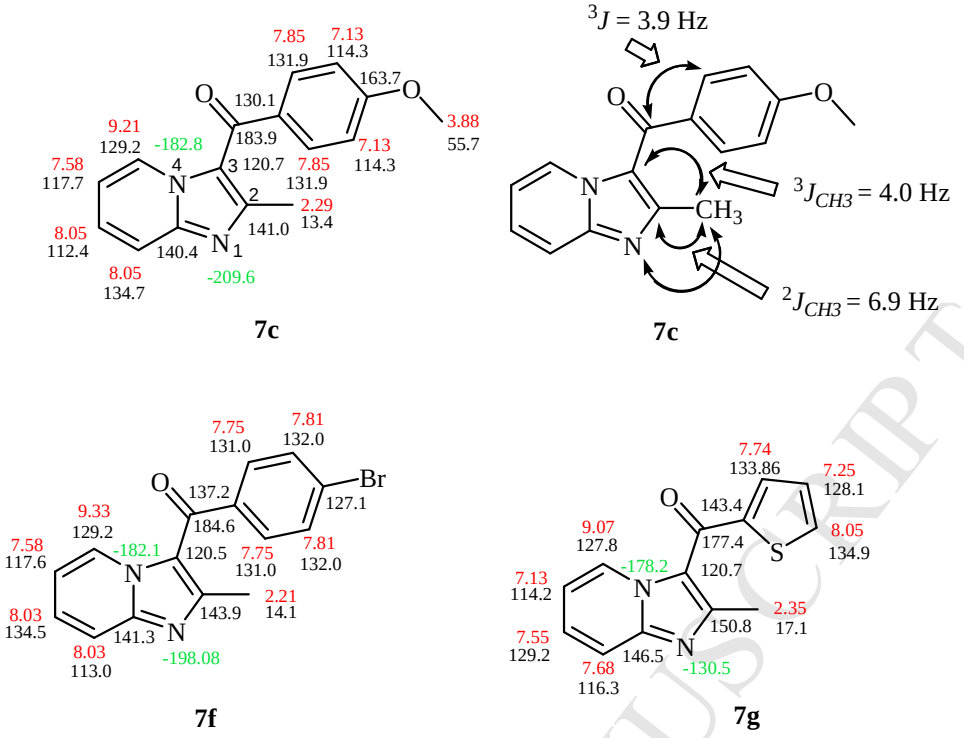


Figure-2 ^{1}H (in red), ^{13}C (in black) and ^{15}N (in green) chemical shifts of compound **7c, 7f** and **7g** and correlation depiction

The (^{1}H-^{13}C) HMBC of compound 1-(4-methoxyphenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone **7c** in **Figure-2** showed cross peaks of methyl protons (δ 2.29) with C-2 (δ 141.0, $^2J_{CH3}$ = 6.9 Hz) and C-3 (δ 120.7, $^3J_{CH3}$ = 4.0 Hz). Further, (^{1}H-^{15}N) HMBC of compound **7c** also showed cross peak of methyl protons (δ 2.29) with N-1 (δ -209.6) thus confirmed the presence of methyl substituent at position-2 of imidazo[1,2-*a*]pyridyl nucleus. Similarly (^{1}H-^{13}C) HMBC of carbonyl carbon at δ183.9 showed cross peak with 2'-H proton (δ 7.85, ^3J = 3.9 Hz) of aryl part indicated the presence of carbonyl carbon with aryl/heteroaryl ring. Had the structure of the isolated compound been corresponding to the other positional isomers **4**, **5** and **6**, then the correlation between methyl protons with N-1 and cross peak of carbonyl carbon with 2'-H proton of aryl part would have been absent. Similar correlation results of (^{1}H-^{13}C) HMBC and (^{1}H-^{15}N) HMBC were observed for the compounds **7f** and **7g** as shown in **Figure-2**.

It is interesting to note that in case of **7c** and **7f**, N-1 was protonated as the value appeared highly upfield[19] at δ -209.6 & δ -198.8 while in case of **7g** it was non-protonated, the signal appeared at δ -130.5. Protonation of **7c** and **7f** is also observed in the ^1J (^{1}H-^{13}C) coupling constant values of C5, C6, C7, C8 when compared with those of **7g**.

Final confirmation of the structure as 1-aryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones isomer **7** was done by X-ray crystallography. Compound **7f** crystallizes in the orthorhombic *Pbca* space group. The asymmetric unit contains two crystallographically different and independent molecules (**Figure-3**),

due to the diverse interactions that each type of them presents. The molecules, named type A and B, are not planar with dihedral angles between the aromatic rings of 60.9(1)º for A molecules, and 55.6(1)º for B molecules.

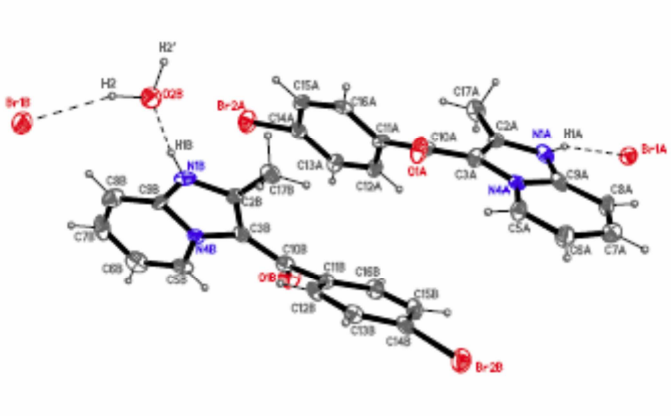


Figure-3 ORTEP plot (20% probability) showing the labeling scheme for compound **7f**

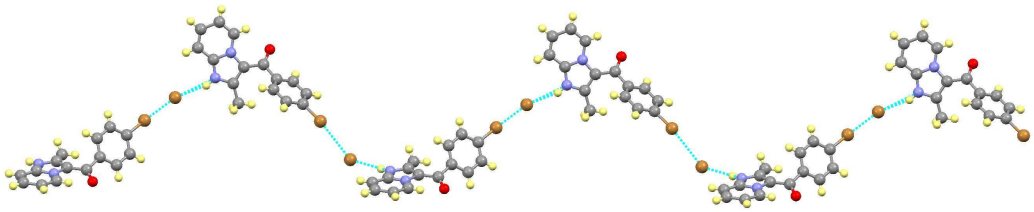
Type A molecules are connected to each other through the bromide ion Br1A that forms a hydrogen bond with the N1AH1A group (**Table-1**) of a molecule, and a Br···Br interaction with the bromine atom of another adjacent molecule (Br1A···Br2A distance of 3.541(2)Å), giving rise to the formation of chains along the *a* axis (**Figure-4**). On the other hand, type B molecules interact not only with the bromide ions Br1B but also with a molecule of water. Thus, being focused on a water molecule, it forms three hydrogen bonds with two different bromide ions Br1B and another one with a N1BH1B group of a type B molecule (**Table-1**), so the bromide ions Br1B interact with two different water molecules, achieving double chains along *b* axis. Besides, contacts between the parallel chains are observed due to additional interactions between the bromide ions Br1B with the Br2B of the neighboring B molecule (distance of 3.584(2) Å) and with the H12B of a phenyl ring (distance of 3.009(1) Å) of a different one, spreading out the dimensionality of the interactions in the *ab* plane (Figure 3b). By the way, there are no significant interactions between type A and B molecules to be noted.

Table-1 Hydrogen bonds for **7f**, $C_{30}H_{26}Br_4N_4O_3$ (Å and °)

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2B)-H(2)...Br(1B)	0.95	2.27	3.179(9)	159.9
O(2B)-H(2')...Br(1B)[a]	0.95	2.34	3.225(9)	154.4
N(1A)-H(1A)...Br(1A)	0.86	2.41	3.226(9)	157.9
N(1B)-H(1B)...O(2B)	0.86	1.87	2.712(12)	167.7

[a] Symmetry transformations used to generate equivalent atoms: -x+3/2, y+1/2, z

a)



b)

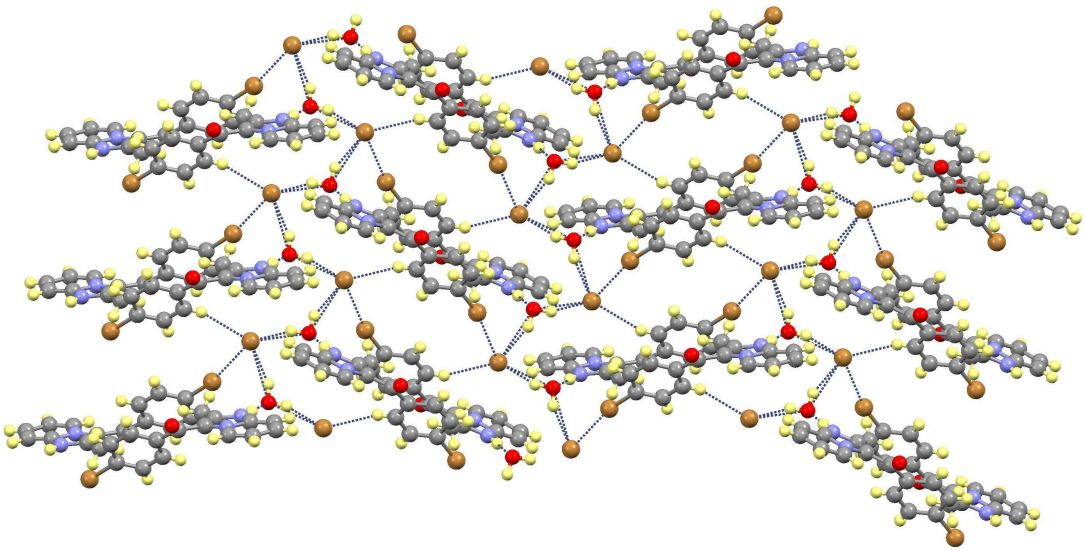
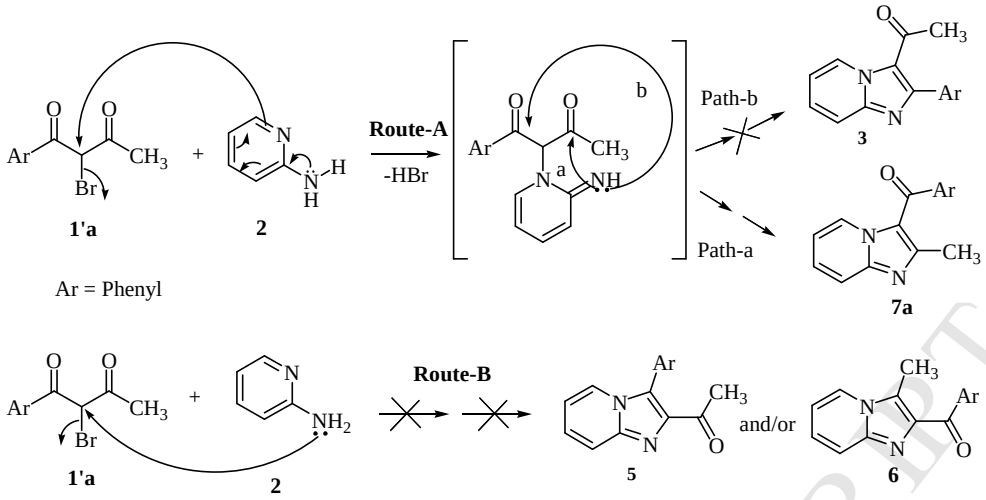


Figure-4 (a) View of the chains formed by A type molecules in **7f**; (b) View along *c* axis showing the 2D interactions that B type molecules, Br1B ions and the water molecules are involved

Mechanism Involved:

The plausible mechanism for this regioselective synthesis of imidazo[1,2-*a*]pyridines **7**(**a-g**) is outlined in **Scheme-3**. It seems that, the reaction by endo nitrogen (ring N) of 2-aminopyridine **2** and 2-bromo dicarbonyl compound **1'a** undergoes initially through the nucleophilic displacement of bromine followed by the nucleophilic addition of imine nitrogen at either of the carbonyl carbon leading to the formation of 2-alkyl/arylimidazo[1,2-*a*]pyridine (**Route-A**).



Scheme-3 Plausible mechanism for regioselective synthesis of imidazo[1,2-*a*]pyridines

In case of non-symmetrical 2-bromo-1,3-diketones after nucleophilic displacement of halogen residue, there remains two electrophilic carbonyl site for nucleophilic addition elimination reaction by the imine nitrogen. Thus there lies the possibility of formation of following two regioisomers. But due to lesser steric crowding around the carbonyl group adjacent to methyl and more electrophilic nature of carbonyl carbon adjacent to methyl group makes it more reactive than carbonyl carbon next to aryl part thus rendering the regioselectivity in the reaction accomplishing **7(a-g)** as the only product. This observation is in consonance with our earlier observation[12g]. Whereas in **Route-B**, nucleophilic displacement of bromine by nitrogen of amino group followed by the nucleophilic addition of endo nitrogen at either of the carbonyl carbon might have led to the formation of 3-alkyl/arylimidazo[1,2-*a*]pyridine whose formation is not observed in our case.

Conclusion:

In the present report, we describe a regioselective synthesis of 1-aryl/heteroaryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones following a simple and mild method. Synthesis involves one-pot condensation of 2-aminopyridine with 1,3-diketones in presence of N-bromosuccinimide (NBS) in DCM by stirring at room temperature. Reaction is found to involve the intermediacy of 2-bromo-1,3-diketones formed from 1,3-diketones on reaction with NBS and has been supported by isolation of intermediate in one case. The structure of the regioisomer has been confirmed unambiguously by the rigorous multinuclear NMR [(^{1}H-^{13}C) HMBC, (^{1}H-^{13}C) HMQC, (^{1}H-^{15}N) HMBC] spectroscopy and X-ray crystallographic studies.

Experimental:

General

Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra for analytical purpose were recorded in $CDCl_3$ on a Bruker instrument at 300 MHz and 75 MHz,

respectively, and chemical shifts were recorded in ppm (δ) downfield from internal standard tetramethylsilane (δ 0.00). Mass spectra were measured in EI mode on a Kratos MS-50 spectrometer at MS Facilities at SAIF, Panjab University, Chandigarh, India. Elemental analyses were also performed at SAIF, Panjab University, Chandigarh, India. All the compounds gave C, H and N analysis within $\pm$ 0.5 of the theoretical values analyzed on Thermoscientfic (FLASH-2000).

2D correlation spectra, (^{1}H-^{13}C) gs-HMQC, (^{1}H–^{13}C) and (^{1}H–^{15}N) gs- HMBC, of compounds **7c**, **7f** and **7g**, were acquired on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 40.56 for ^{15}N) spectrometer with a 5-mm inverse-detection H–X probe equipped with a z-gradient coil, at 300 K and processed using standard Bruker NMR software and in non-phase-sensitive mode. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms. Selected parameters for (^{1}H–^{13}C) gs-HMQC and gs-HMBC spectra were spectral width 3500 Hz for ^{1}H and 20.5 kHz for ^{13}C, 1024 x 256 data set, number of scans 2 (gs-HMQC) or 4 (gs-HMBC) and relaxation delay 1 s. The FIDs were processed using zero filling in the F1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation. In the gs- HMQC experiments GARP modulation of ^{13}C was used for decoupling. Selected parameters for (^{1}H-^{15}N) gs-HMBC spectra were spectral width 3500 Hz for ^{1}H and 12.5 kHz for ^{15}N, 1024 x 512 data set, number of scans 8, relaxation delay 1s, 60-100 ms delay for the evolution of the ^{15}N-^{1}H long-range coupling. The FIDs were processed using zero filling in the *F*1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation.

Synthesis

1,3-Diketones[20] **1a-g** were prepared according to literature procedure and 2-aminopyridine (**2**) was available commercially.

General procedure for one-pot synthesis of 1-aryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones (7 a-g) :

To a solution of 1,3-diketones **1a-g** (1.0 mmol) in DCM (10 mL) was added NBS (0.177g, 1.0 mmol) and mixture was allowed to stir at rt for 30 min. Subsequently, 2-aminopyridine **2** (0.094g, 1.0 mmol) was added and reaction mixture was maintained at rt with stirring. The reaction was monitored with TLC. On completion of reaction (4 hr), excess DCM was distilled off in vacuo and the residue was washed with aq. $NaHCO_3$ and extracted with DCM. Organic layers were combined, dried over anhyd. Na_2SO_4 and excess solvent was distilled off. The residual mass was recrystallized from ethanol and **7a-g** was obtained in 71 to 81% yield.

1-Phenyl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7a)

Creamy white solid.

Mp 62-64ºC, Lit. Mp 82-84ºC[14].

Yield: 75%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.51(d, 1H, *J* = 6.6 Hz, 5-H), 8.48 (d, 1H, *J* = 8.7 Hz, 8-H), 7.98-8.03(m, 1H, 7-H), 7.73-7.77(m, 3H, Ph 2,4,6-H), 7.59-7.64 (m, 2H, Ph 3,5-H), 7.52-7.57 (m, 1H, 6-H), 2.51 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 14.12, 113.15, 118.40, 121.12, 129.41, 129.82, 133.80, 135.57, 138.55, 141.29, 143.35, 186.12.

MS (EI): 237 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86 % Found: C, 75.86; H, 4.92; N, 11.52 %.

1-(4-Methylphenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7b)

Creamy white solid.

Mp 116-118ºC.

Yield: 76%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.45 (d, 1H, *J* = 6.9 Hz, 5-H), 7.68 (d, 1H, *J* = 8.7 Hz, 8-H), 7.61 (d, 2H, *J* = 7.8 Hz, 4-CH_3Ph 2,6-H), 7.45-7.51 (m, 1H 7-H), 7.32 (d, 2H, *J* = 7.8 Hz, 4-CH_3Ph 3,5-H), 7.02-7.07 (m, 1H, 6-H), 2.47 (s, 3H, 2-CH_3), 2.23 (s, 3H, 4-CH_3Ph).

^{13}C NMR (75 MHz, $CDCl_3$): 17.41, 21.64, 114.18, 116.52, 121.54, 128.44, 128.67, 129.03, 129.13, 129.26, 129.72, 137.52, 142.55, 147.34, 152.85, 186.89.

MS (EI): 251 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19 % Found: C, 76.43; H, 5.22; N,75.71 %.

1-(4-Methoxyphenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7c)

Creamy white solid.

Mp 56-58ºC.

Yield: 78%.

^{1}H NMR (400 MHz, DMSO): δ = 9.21 (ddd, 1H, ^{3}J = 6.9 Hz, ^{4}J = ^{5}J = 1.0 Hz, 5-H), 8.05 (m, 2H, 7, 8-H), 7.85 (m, 2H, 4-OCH_3Ph 2,6-H), 7.58 (ddd, 1H, ^{3}J = 6.9 Hz, ^{3}J = 6.1 Hz, ^{4}J = 2.2 Hz, 6-H), 7.13 (m, 2H, 4-OCH_3, Ph 3,5-H), 3.88 (s, 3H, 4-OCH_3Ph), 2.29 (s, 3H, 2-CH_3).

^{13}C NMR (100 MHz, DMSO): 13.4, 55.7, 112.4, 114.3, 117.7, 120.7, 129.2, 130.1, 131.9, 134.7, 140.4, 141.0, 163.7, 183.9.

MS (EI): 267 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52 % Found: C, 71.94; H, 5.11; N, 10.30 %.

1-(4-Fluorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7d)

Light yellow solid.

Mp 108-110ºC.

Yield: 80%.

^{1}H NMR (300 MHz, DMSO): δ = 9.33 (d, 1H, *J* = 7.2 Hz, 5-H), 7.93-7.94 (m, 2H, 7,8-H), 7.85-7.87 (m, 2H, 4-FPh 2,6-H), 7.41-7.51(m, 3H, 6-H, 4-FPh 3,5-H), 2.18 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, DMSO): 14.2, 113.2, 116.6 (^2J_F=21.9), 118.3, 121.1, 129.8, 132.6 (^3J_F=9.1), 135.1 (^4J_F=3.0), 135.3, 141.4, 143.3, 165.5 (^1J_F=252.1), 184.70.

MS (EI): 255 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{11}FN_2O$: C, 70.86; H, 4.36; N, 11.02 % Found: C, 70.23; H, 4.11; N, 10.92 %.

1-(4-Chlorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7e)

White solid.

Mp 142-144ºC.

Yield: 79%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.47 (d, 1H, *J* = 6.9 Hz, 5-H), 8.41 (d, 1H, *J* = 8.7 Hz, 8-H), 7.94-7.99 (m, 1H, 7-H), 7.72 (d, 2H, *J* = 8.7 Hz, 4-ClPh 2,6-H), 7.59 (d, 2H, *J* = 8.7 Hz, 4-ClPh 3,5-H), 7.48-7.53 (m, 1H, 6-H), 2.52 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 14.68, 113.66, 118.01, 121.01, 129.53, 129.69, 131.33, 134.77, 137.47, 138.43, 144.82, 184.94.

MS (EI): 271 $[M+H]^+$, 273 $[M+H+2]^+$ (3:1).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35 % Found: C, 66.42; H, 3.95; N, 10.21 %.

1-(4-Bromophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7f)

White solid.

Mp 136-138ºC.

Yield: 77%.

^{1}H NMR (400 MHz, DMSO): δ = 9.33 (ddd, 1H, ^3J = 6.9 Hz, ^4J = ^5J = 1.1 Hz, 5-H), 8.03 (m, 2H, 7, 8-H), 7.81 (d, 2H, 4-BrPh 3,5-H), 7.75 (m, 2H, 4-BrPh 2,6-H), 7.58 (d, 1H, ^3J = 6.9 Hz, ^3J = 6.1 Hz, ^4J = 2.3 Hz 6-H), 2.21 (s, 3H, 2-CH_3).

^{13}C NMR (100 MHz, DMSO): 14.1, 113.0, 117.6, 120.5, 127.1, 129.2, 131.0, 132.0, 134.5, 137.2, 141.3, 143.9, 184.6.

MS (EI): 315 $[M+H]^+$, 317 $[M+H+2]^+$ (1:1).

Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89 % Found: C, 56.98; H, 3.47; N, 8.75 %.

1-(Thien-2-yl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7g)

Light brown solid.

Mp 114-116ºC.

Yield: 71%.

^{1}H NMR (400 MHz, DMSO): δ = 9.07 (ddd, 1H, ^{3}J = 6.9 Hz, ^{4}J = ^{5}J = 1.2 Hz, 5-H), 8.05 (m, 1H, thienyl 5-H), 7.74 (m, 1H, thienyl 3-H),7.68 (m, 1H, 8-H), 7.55 (m, 1H, 7-H), 7.25 (m, 1H, thienyl 4-H), 7.13 (ddd, 1H, ^{3}J =, ^{3}J = 6.9 Hz, ^{4}J = 1.3 Hz, 6-H), 2.35 (s, 3H, 2-CH_3).

^{13}C NMR (100 MHz, DMSO): 17.1, 114.2, 116.3, 120.7, 127.8, 128.1, 129.2, 133.86, 134.09, 143.4, 146.5, 150.8, 177.4.

MS (EI): 243 $[M+H]^+$.

Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56 % Found: C, 64.40; H, 4.06; N, 11.49s %.

General procedure for the step-wise synthesis of 1-aryl-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanones (7b) :

2-bromo-1-(4-methylphenyl)butane-1,3-dione (1'b) :

A solution of 1-(4-methylphenyl)butane-1,3-dione **1b** (0.176g, 1.0 mmol) and NBS (0.177g, 1.0 mmol) was stirred in DCM at room temperature (rt) and the reaction was monitored with TLC at regular intervals. On completion of reaction (1 hr), the reaction mixture was washed with water and extracted with DCM. Organic extracts were combined, dried over anhyd. Na_2SO_4 and concentrated in vacuo to a minimum and **1'b** was obtained.

Pale Orange solid.

Mp 50-52ºC[21].

Yield: 60%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81-7.91 (d, 2H, *J* = 8.4 Hz, Ph 3,5-H), 7.30-7.33 (d, 2H, *J* = 8.1 Hz, Ph 2,4-H), 5.61 (s, 1H, CHBr), 2.46 (s, 3H, Ph-CH_3), 2.45 (s, 3H, $COCH_3$).

1-(4-Methylphenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (7b) :

2-Aminopyridine **2** (0.094g, 1.0 mmol) was added to a solution of 2-bromo-1-(4-methylphenyl)butane-1,3-dione (1'b) (0.255g, 1.0 mmol) in DCM and mixture was allowed to stir at rt. The reaction was monitored with TLC. On completion of reaction (4 hr), excess DCM was removed in vacuo and the residue was washed with aq. $NaHCO_3$ and extracted with DCM. Organic layers were combined, dried over anhyd. Na_2SO_4 and excess solvent was distilled off. The residual mass was recrystallized from ethanol and **7b** was obtained.

Creamy white solid.

Yield: 45% ; Overall Yield: 27%.

X-Ray data collection and structure refinement

Suitable crystals for X-ray determination of compound **7f** have been obtained from ethanol. Data collection was carried out at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ= 0.71073 Å) operating at 50 kV and 20 mA. The data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 10s covered 0.3 in ω. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. A summary of the fundamental crystal and refinement data is given in **Table 2**. The structure was solved by direct methods and refined by full-matrix least-square procedures on F^2 (SHELXL-97)[22].

Table-2 Crystal data and structure refinement for $C_{30}H_{26}Br_4N_4O_3$ (**7f**)

CCDC-code	991345
Empirical formula	$[C_{30}H_{26}Br_4N_4O_3]$
Formula weight	810.19
Crystal system	Orthorhombic
Space group	*Pbca*
Space group number	61
a / Å	25.378(2)
b / Å	8.0199(8)
c / Å	30.457(3)
α (º)	90.0
β (º)	90.0
γ (º)	90.0
V / Å^3	6198.9(10)
Z	8
F(000)	3184
ρ_c / g cm^{-3}	1.736
μ / mm^{-1}	5.232
Data collected	(–20, –9, –36) to (30, 9, 32)
θ range (º)	1.34 to 25.00
Reflections collected	45293
Independent reflections	5470 (R_{int} = 0.2053)
Completeness to maximum *θ* (%)	100.0%
Data / restrainsts / parameters	5470 / 0 / 372
Observed reflections [$I > 2\sigma(I)$]	1881
R^a	0.0567
$R_{wF}{}^b$	0.1641

$^a\Sigma[|F_o| - |F_c|] / \Sigma[|F_o|]$. $^b \{\Sigma[w(F_o{}^2 - F_c{}^2)^2] / \Sigma[w(F_o{}^2)^2]\}^{1/2}$

All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in their calculated positions and refined riding on the respective carbon atoms. Further crystallographic details for the structure reported in this paper may be obtained from the Cambridge Crystallographic Data Center, on quoting the depository number CCDC- 991345.

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