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Bromodimethylsulfonium bromide (BDMS) catalyzed synthesis of imidazo[1,2-*a*]pyridine derivatives and their fluorescence properties

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ABSTRACT

A convenient synthetic protocol for the synthesis of imidazo[1,2-*a*]pyridine has been developed by employing one-pot three-component Ugi reaction by employing aromatic amidine, aromatic aldehyde, and isocyanide using 5 mol % of bromodimethylsulfonium bromide (BDMS) at room temperature. In addition, they also exhibit interesting fluorescence properties, which may be useful for fluorescent probe. Mild reaction conditions, non-aqueous work-up procedure, good yields, short reaction time, and no need of chromatographic separation are some of the salient features of the present protocol.

Multicomponent reactions (MCRs) are found to be a useful strategy for the construction of architecturally complex molecules having a wide range of biological activities from the readily available starting materials in a single step.[1] Due to their simplicity, high selectivity, good yield, superior atom-economy, high variability, less time consuming, and avoidance of costly purification processes,[2,3] these reactions have gained considerable attention in recent times. The catalysts also play a crucial role in various multi-component reactions in determining the nature of the product, yield, reaction time, and selectivity.

Heterocyclic compounds always attribute remarkable attention in pharmaceutical industry due to their wide therapeutic values. Among them, imidazo[1,2-*a*]pyridine derivatives display a diverse range of biological activities such as antiviral,[4] antiulcer,[5a] hypnotic, and diabetic agent[5b] as depicted in Figure 1.

These compounds can be prepared traditionally in two ways: (i) by two component condensation of an amidine and α-haloketones[4,5a] (ii) based on three-component Ugi reaction (3-CR) of aromatic amidines with aromatic aldehyde and isocyanide.[6] For the second approach, numerous catalysts have been used over the years such as using microwave irradiation in the presence of Montmorillonite clay K10[7a] or $Sc(OTf)_3$[7b] solid supported *p*-toluenesulfonic acid[8a] and glyoxalic acid[8b] or $Sc(OTf)_3$,[8c] $ZnCl_2$,[9] and ionic liquid.[10] Recently, Adib et al. reported the synthesis of imidazo[1,2-*a*]pyridine scaffolds using Ugi reaction (3-CR) without any catalyst[11] and by employing modified three-component Ugi reaction (3-CR) of aromatic amidines, benzyl halide, and isocyanide in the presence of DMSO and K_2CO_3.[11b] However, some of the above methods have some demerits such as the requirement of expensive and excess amount of catalyst,[6] longer time,[6,7a,11] difficulties in work-up procedure, and harsh reaction conditions.[7] Though these protocols are quite useful, still there is a further scope to develop a new methodology which might work even under milder reaction conditions. Recently we have reported[12] the usefulness of bromodimethylsulfonium bromide (BDMS) as a catalyst as well as brominating reagent in the organic synthesis. As a part of our ongoing efforts on the development of new synthetic protocols for the synthesis of biologically active heterocyclic compounds through MCRs,[13] we conceived that BDMS can be used as an efficient catalyst for the synthesis of imidazo[1,2-*a*]pyridine derivatives. In this Letter, three-component condensation (3CC) of aromatic aldehydes, aromatic amidines, and isocyanides is reported for the synthesis of imidazo[1,2-*a*]pyridine derivatives using BDMS as a catalyst as shown in Scheme 1.

For the present study, the catalyst bromodimethylsulfonium bromide (BDMS) was prepared by following the literature procedure.[12a] In the beginning, the model reaction of *p*-chlorobenzalde-

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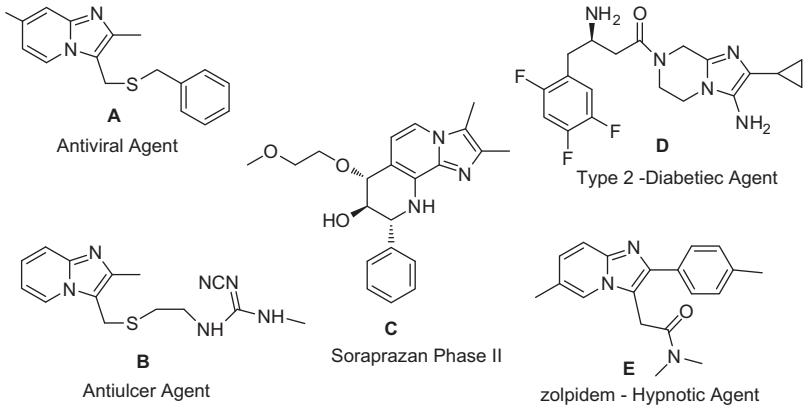
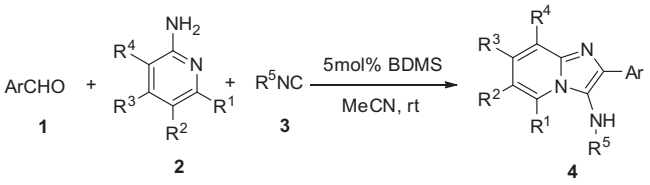


Figure 1. Some of the biologically active compounds containing imidazo[1,2-*a*]pyridine framework.



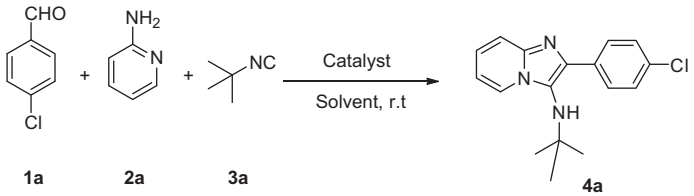
Amidines	Isocyanides
2a: R^1= R^2=R^3=R^4=H	**3a:** *tert*-Butyl
2b: R^1=R^3=R^4=H, R^2=Me	**3b:** Cyclohexyl
2c: R^1= R^2=R^3= H, R^4=Me	**3c:** 2-Morpholinoethyl
2d: R^1=R^3=Me,R^2=Br,R^4=H	

Scheme 1. Synthesis of imidazo[1,2-*a*]pyridine derivatives.

hyde (**1a**), amidine (**2a**) and *tert*-butyl isocyanide (**3a**) was conducted to find out the optimal reaction conditions and the results were mentioned in Table 1. We executed various trial reactions and noticed that the reaction provided best result in the presence of 5 mol % BDMS in acetonitrile at room temperature (Table 1, entry 10). Other Lewis acids such as ceric ammonium nitrate (CAN) and $Cu(OTf)_2$ in MeCN (Table 1, entries 2 and 3) were also examined, which afforded relatively lower yield of compound **4a**. To examine the suitability of various solvent(s) system, it was observed that acetonitrile gave the best result in terms of reaction time and yield.

After optimizing the reaction conditions, a mixture of 4-bromobenzaldehyde, 2-aminopyridine, and *tert*-butyl isocyanide was kept for stirring with 5 mol % BDMS at room temperature and the desired product **4b** was obtained in 85% yield. Likewise, a mixture of 3-hydroxybenzaldehyde, 2-aminopyridine, and *tert*-butyl isocyanide also provided the required product **4c** in 90% yield under identical reaction conditions. For generality of the present protocol, we have scrutinized several reactions with various aromatic aldehydes having substituent in the aromatic ring with 2-amino-5-methylpyridine and *tert*-butyl isocyanide smoothly under similar reaction conditions and all these reactions afforded the products **4d–k** in good yields. It was noted that the aldehyde containing electron-withdrawing group takes relatively shorter reaction time than the aromatic aldehyde having electron-donating group (Table 1, entry 6).

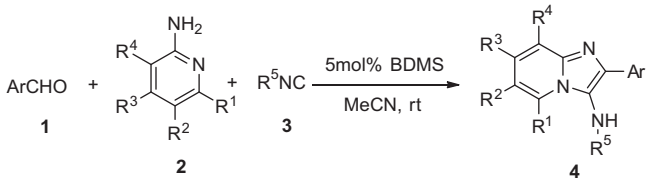
Table 1
Optimization of the reaction conditions[a]

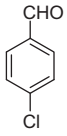
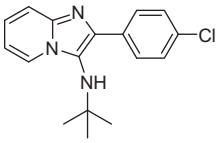
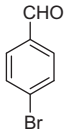
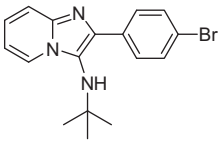
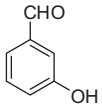
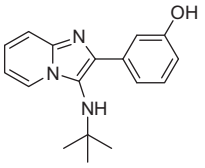
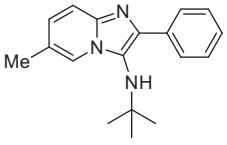
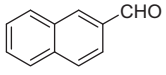
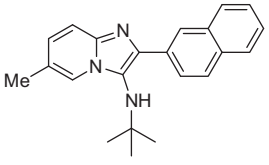
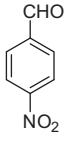
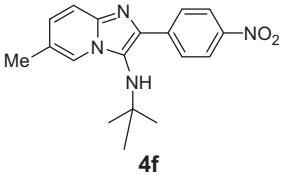
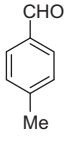
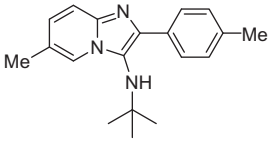
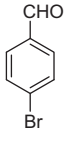
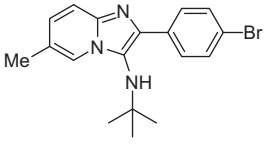


Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	—	CH_3CN	14	26
2	10 mol % CAN	CH_3CN	12	64
3	10 mol % $Cu(OTf)_2$	CH_3CN	9	55
4	5 mol % BDMS	MeOH/DCM	3	75
5	5 mol % BDMS	CH_3CN/MeOH	2	85
6	5 mol % BDMS	CH_3CN/DCM	2.5	80
7	5 mol % BDMS	THF	3.5	77
8	5 mol % BDMS	1.4 Dioxane	3	72
9	5 mol % BDMS	DMF	3.5	68
10	5 mol % BDMS	CH_3CN	0.5	95

[a] The reaction was performed using 1 mmol scale of *p*-chlorobenzaldehyde, 2-amino pyridine, and *tert*-butyl isocyanide at room temperature.
[b] Isolated yield.

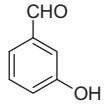
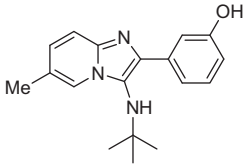
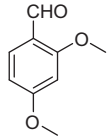
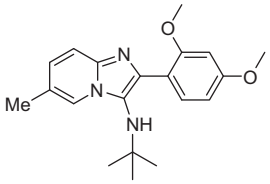
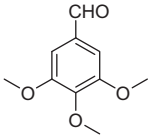
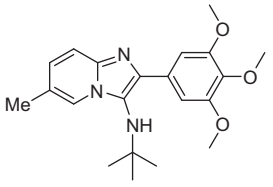
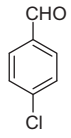
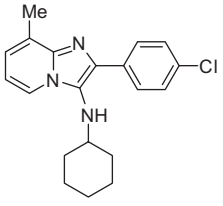
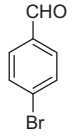
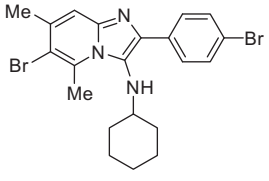
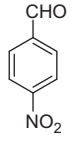
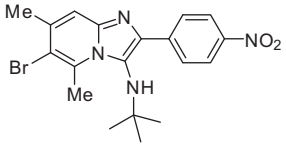
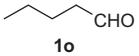
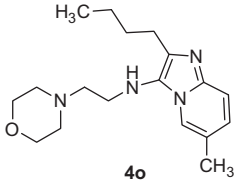
Table 2
Synthesis of imidazo[1,2-*a*]pyridines[15]



Entry	Aldehyde	Amidine	Isocyanide	Product[a]	Time (h)	Yield[b] (%)
1	 **1a**	**2a**	**3a**	 **4a**	2	95
2	 **1b**	**2a**	**3a**	 **4b**	2	85
3	 **1c**	**2a**	**3a**	 **4c**	2	90
4	 **1d**	**2b**	**3a**	 **4d**	1.5	96
5	 **1e**	**2b**	**3a**	 **4e**	1	93
6	 **1f**	**2b**	**3a**	 **4f**	0.5	94
7	 **1g**	**2b**	**3a**	 **4g**	1	95
8	 **1h**	**2b**	**3a**	 **4h**	2.5	89

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Amidine	Isocyanide	Product[a]	Time (h)	Yield[b] (%)
9	 **1i**	**2b**	**3a**	 **4i**	1	92
10	 **1j**	**2b**	**3a**	 **4j**	2	85
11	 **1k**	**2b**	**3a**	 **4k**	2.5	88
12	 **1l**	**2c**	**3b**	 **4l**	1.5	90
13	 **1m**	**2d**	**3b**	 **4m**	1.5	87
14	 **1n**	**2d**	**3a**	 **4n**	1	96
15	 **1o**	**2b**	**3c**	 **4o**	2.5	70

[a] All the reaction was performed using (1 mmol) aldehyde, (1 mmol) amidine, and (1 mmol) isocyanide.

[b] Isolated yield.

To verify further the scope of the present protocol, the reactions were also conducted with 2-amino-3-methylpyridine, chlorobenzaldehyde, and cyclohexylisocyanide in the presence of 5 mol % BDMS at room temperature, which gave the desired product in good yield. Lastly, the reactions were carried out with sterically hindered 2-amino-5-bromo-4,6-dimethylpyridine with aromatic

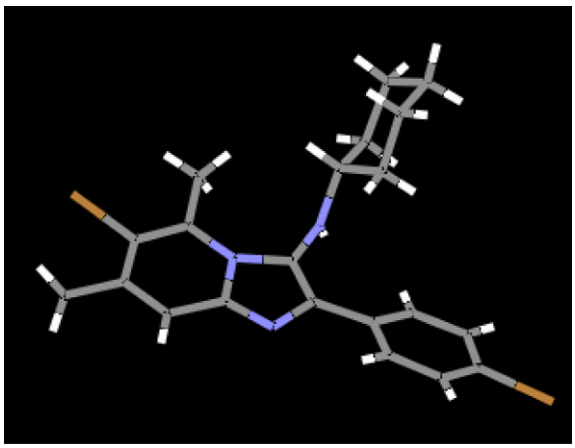


Figure 2. X-ray crystal structure of **4m** (CCDC No. 848594).

aldehydes and isocyanides under identical conditions and they also gave products **4m** and **4n** in 87% and 96% yields, respectively. To verify the present protocol with aliphatic aldehyde, we have performed reaction with valeraldehyde, 2-amino-5-methylpyridine and 2-morpholinoethyl isocyanide in the presence of 5 mol % BDMS under identical reaction conditions and it provided the desired product **4o** in 70% yield (Table 2, entry 15). From these results, it is quite obvious that the present protocol is a general one, which works with various amidines as well as with different aromatic/aliphatic aldehydes.

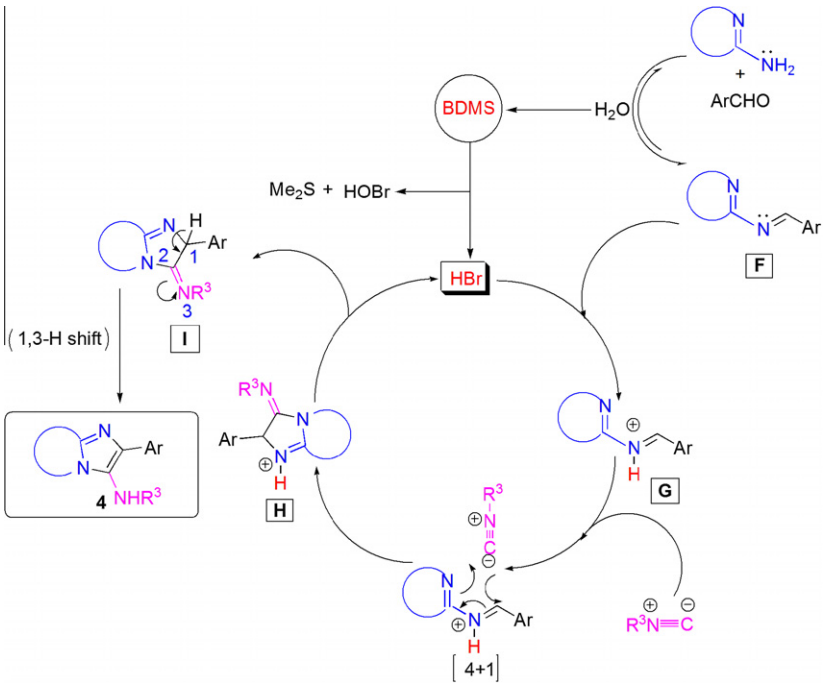
All the isolated products were fully characterized by IR, and NMR spectroscopy. In addition, the structure of compound **4m** was also determined using single-crystal X-ray data (as shown in Fig. 2).[16]

The formation of imidazo[1,2-*a*]pyridine can be explained as follows: Initially aromatic aldehyde reacts with amidine to form imine **F** and water. The released water molecule reacts with BDMS which leads to the formation of dimethyl sulfide, HOBr, and HBr. Then, the imine undergoes protonation with the liberated HBr to form **G**, which reacts instantly with isocyanide in a [4+1] cycloaddition manner to give intermediate **I**. The final product imidazo[1,2-*a*]pyridines **4** was obtained from the intermediate **I** by 1,3-hydrogen shift, as shown in Scheme 2. To compare the efficiency of the present protocol, we have also examined the reaction with a mixture of 4-chlorobenzaldehyde, 2-aminopyridine, and *tert*-butyl isocyanide in the presence of 48% aqueous HBr (0.1 mL) at room temperature. The desired product **4a** was obtained in 65% yield after 4 h of stirring, which is lower as compared to BDMS-catalyzed reaction.

Recently, Balakirev et al. reported that some of the imidazo[1,2-*a*]pyridine derivatives are potential candidate for fluorescent probes, which can be used for fluorescence imaging in clinical diagnostics and biomedical research.[14] Therefore, we felt that the compounds prepared by us may also exhibit similar properties and their results of the photophysical properties of the imidazo[1,2-*a*]pyridine are summarized in Table 3. Moreover, the UV–visible spectra of the imidazo[1,2-*a*]pyridine derivatives contain intense absorption maxima at 250 ± 5 and at 335 ± 2 nm. At C2 position of the imidazo[1,2-*a*]pyridine which bears a chlorine substituent in the aromatic ring **4a** results in a shift of the absorption maxima to longer wavelength. These compounds exhibit Stokes shift in the range of 122–137 nm.

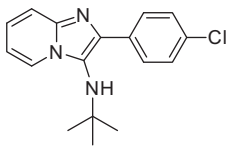
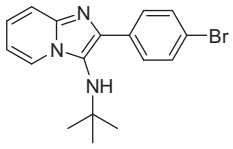
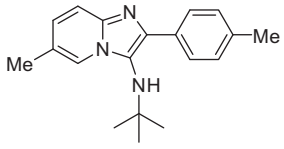
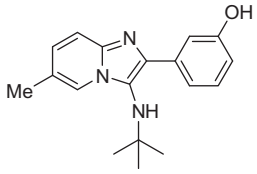
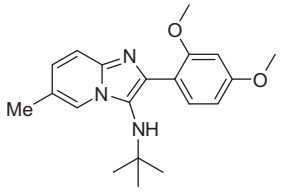
The output of the fluorescence results are displayed in Table 3, which show that among the electron donating group on the aromatic ring at C2 position of the imidazo[1,2-*a*]pyridine, 2,4-OMe group on the aromatic ring **4j** enhances the fluorescence wavelength maxima.

Furthermore, the fluorescence of the imidazo[1,2-*a*]pyridine derivatives **4** is shown in Figures 3 and 4, respectively.



Scheme 2. Plausible mechanism for the formation of imidazo[1,2-*a*]pyridines.

Table 3
Photo physical data of imidazo[1,2-*a*]pyridine in CH_2Cl_2

Entry	Imidazo[1,2-*a*]pyridine	Absorption[a]		Fluorescence[b] λ_{em}[b]
		λ_{abs} (nm)	ε (M^{-1} cm^1)	
1	 **4a**	253 337	133,400 28,110	460
2	 **4b**	254 336	166,120 35,200	458
3	 **4g**	245 335	230,100 85,500	461
4	 **4i**	249 332	58,630 13,050	467
5	 **4j**	252 333	47,430 13,560	470

[a] Measured at a concentration of 1.0×10^{-5} mol dm^{-3} at 25 °C.
[b] Emission maxima upon excitation at 320 nm.

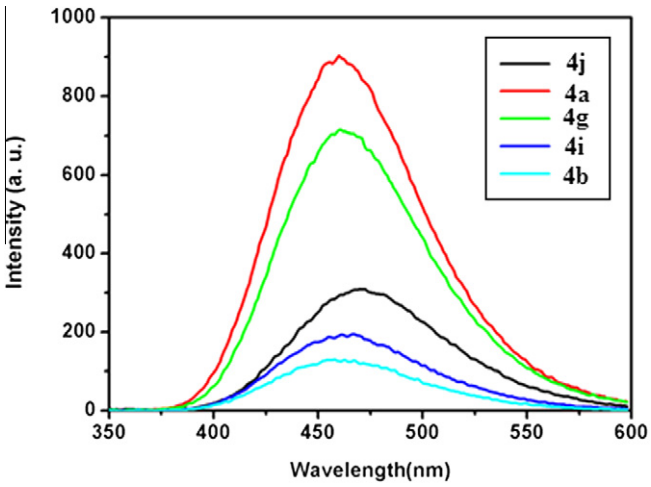


Figure 3. Fluorescence spectra of imidazo[1,2-*a*]pyridine derivatives.

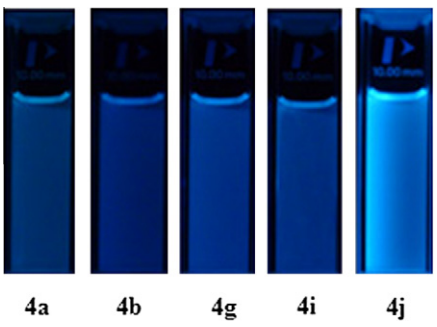


Figure 4. Fluorescence of **4** in CH_2Cl_2.

In summary, we have devised a simple and an efficient protocol for the one-pot synthesis of imidazo[1,2-*a*]pyridine derivatives catalyzed by BDMS under mild reaction conditions. Moreover, the present protocol possesses several unique merits such as simplicity, non aqueous work-up, and most importantly

high yield of the products. These new classes of fluorescence imidazo[1,2-*a*]pyridine derivatives may be of great interest in clinical diagnostics and biomedical application in future. As a result, this protocol may provide an access to a diverse array of medicinal scaffold of imidazoheterocycles. Furthermore, the studies on the fluorescence properties of the imidazo[1,2-*a*]pyridine in biomedical application is under process, which will be reported in due course of time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.078.

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15. *General procedure for the synthesis of imidazo[1,2-a]pyridine*: A mixture of aromatic aldehyde (1 mmol), amidine (1 mmol), and isocyanide (1 mmol) was taken in 2 mL acetonitrile. Then, the catalyst bromodimethylsulfonium bromide (0.011 g, 0.05 mmol) was added into it and the reaction mixture was kept for stirring at room temperature till the completion of the reaction as indicated by TLC. The solid product came out slowly which was filtered through a Buchner funnel and the solid precipitate was washed with acetonitrile. Finally it was dried under reduced pressure.
Spectral data of some of the compounds: *N-tert-butyl-2-(4-chlorophenyl)H-imidazo[1,2-a]pyridin-3-amine* (***4a***)*:* Brown solid: mp 146 °C. IR (KBr): 2961, 2925, 2854 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H), 3.0 (br s, NH, 1H), 6.70 (t, J = 6.8 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 56.5, 111.5, 117.4, 123.5, 123.6, 124.3, 128.5, 129.4, 133.1, 133.9, 138.4, 142.1. Anal. Calcd for $C_{17}H_{18}ClN_3$: C, 68.11; H, 6.05; N, 14.02. Found: C, 67.95; H, 5.99; N, 13.91. *N-tert-Butyl-6-methyl-2-phenylH-imidazo[1,2-a]pyridin-3-amine* (***4d***)*:* White solid: mp 215–217 °C. IR (KBr): 3289, 2968, 2917, 1604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.25 (s, 3H), 3.0 (br s, *NH*, 1H), 6.90 (d, J = 9.2 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.31–7.39 (m, 3H), 7.82 (d, J = 7.6 Hz, 2H), 7.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 30.4, 56.5, 116.8, 121.0 (2C), 121.3, 123.4, 127.3, 128.2, 128.3, 135.6, 139.5, 141.3. Anal. Calcd for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.13; H, 7.50; N, 14.96. *6-Bromo-2-(4-bromophenyl)-N-cyclohexyl-5,7-dimethylH-imidazo[1,2-a]pyridin-3-amine* (***4m***)*:* White solid: mp 191 °C. IR (KBr): 2928, 2851, 1633 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01–1.72 (m, 10H), 2.37–2.44 (m, 1H), 2.68 (br s, *NH*, 1H), 3.14 (s, 3H), 3.45 (s, 3H), 7.52 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 24.1, 24.9, 25.8, 33.2, 58.6, 114.7, 114.8, 121.5, 127.0, 129.3, 131.5, 133.7, 134.8, 135.5, 138.4, 142.3. Anal. Calcd for $C_{21}H_{23}Br_2N_3$: C, 52.85; H, 4.86; N, 8.80. Found: C, 52.68; H, 4.79; N, 8.70.
16. Complete crystallographic data of **4m** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 848594 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk.