A Facile Access to 2-Methylthio/Alkoxy/Amino-3-acylimidazo[1,2-*a*]pyridines Based on Cupric Chloride Promoted Oxidative Ring Closure of α-Oxoketene N,S-, N,O-, and N,N-Acetals

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Synthesis of imidazo[1,2-*a*]pyridines and their analogues has attracted significant attention in recent years as this class of compounds exhibit a broad range of pharmacological activity.[1−10] Substituted imidazo[1,2-*a*]-pyridines have been recently identified as a new generation of potential antiviral agents in place of structurally related benzimidazole derivatives, such as Enviroxime, which failed as antiviral drugs in clinical trials because of their poor bioavailability and undesirable side effects.[11] The pharmacological profile of imidazo[1,2-*a*]pyridines is shown to be critically dependent on the nature of substituents at 2 and 3 positions.[2,11a] Thus there is a definite need to develop a more structurally flexible method for the synthesis of this class of compounds.

The most common approach for the synthesis of imidazo[1,2-*a*]pyridines involves construction of imidazole ring on suitably substituted pyridine precursors such as 2-aminopyridines[12−14] (Tschitschibabin reaction), 2-halo-1-phenacyl/alkyl pyridinium salts,[15−17] pyridinium azomethine ylides,[18] and other derivatives.[18b,19,20] Approaches based on the use of substituted imidazoles as starting materials to construct the imidazopyridine nucleus have also been described.[3,21,22] However, most of these methods suffer from drawbacks such as low yields, difficult starting materials involving tedious work up procedure, lengthy sequences, and lack of generality for incorporation of desired substituent in the imidazopyridine nucleus. Therefore reactions involving direct electrophilic substitution or Ullmann coupling on an imidazopyridine ring have been developed recently for regiospecific introduction of acyl,[23] aryl, and alkylthio groups[24] which have been recognized for their distinguishing features in structure−activity relationship studies. During the course of our continued interest on the synthetic application of polarized ketene dithioacetals,[25] we have recently described the synthesis of novel (2-pyridylamino)-N,S- and N,N-acetals via conjugate displacement on various α-oxoketene dithioacetals by 2-(lithioamino)pyridine.[26] Ready availability of these N,S- and N,N-acetals and current increasing interest in the synthesis of imidazo[1,2-*a*]-pyridine derivatives for structure−activity studies prompted us to investigate a new methodology for imidazole annulation by intramolecular ring closure of these intermediates. We herein describe a facile route to 3-aroylimidazo[1,2-*a*]pyridines with a range of function-

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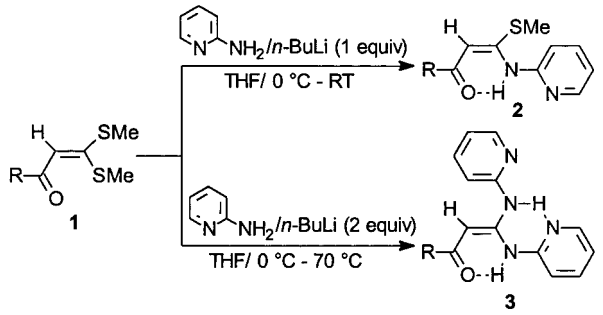
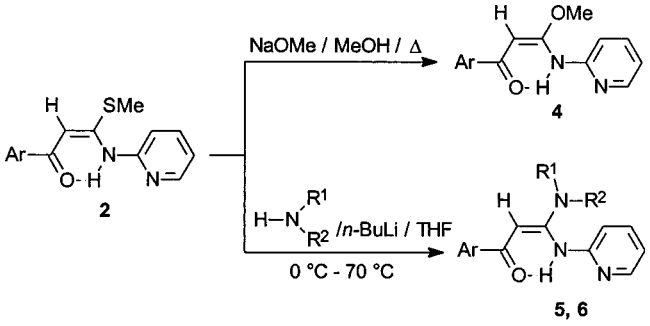
Scheme 1



1	R	2	Yield %	1	R	3	Yield %
1a	C_6H_5	**2a**	92	**1a**	C_6H_5	**3a**	79
1b	4-MeC_6H_4	**2b**	90	**1b**	4-MeC_6H_4	**3b**	81
1c	4-ClC_6H_4	**2c**	90	**1c**	4-ClC_6H_4	**3c**	67
1d	4-$MeOC_6H_4$	**2d**	93	**1d**	4-$MeOC_6H_4$	**3d**	68
1e	2-Furyl	**2e**	88				
1f	2-Thienyl	**2f**	89				

Scheme 2



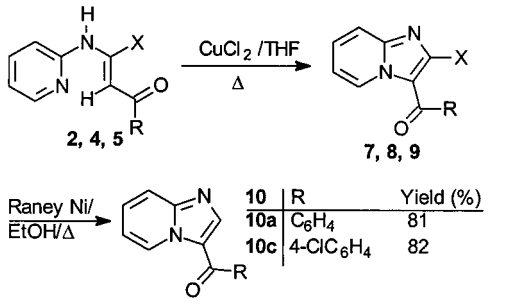
2	Ar	R^1	R^2	4,5,6	Yield %
2c	4-ClC_6H_4	-	-	**4c**	71
2d	4-$MeOC_6H_4$	-	-	**4d**	64
2a	C_6H_5	$-(CH_2)_5-$		**5a**	80
2a	C_6H_5	$-(CH_2)_2-O-(CH_2)_2-$		**5b**	81
2a	C_6H_5	C_6H_5	H	**6a**	78
2b	4-MeC_6H_4	C_6H_5	H	**6b**	77

alities at 2 position through an unusual cupric chloride assisted oxidative ring closure of α-oxoketene N,S-, N,N-, and N,O-acetals.

The desired N,S- **(2a−f)** and N,N-acetals **(3a−d)** were prepared in high yields according to our earlier reported procedure,[26] by displacement reaction on α-oxoketene S,S-acetals **(1a−f)** with either 1 or 2 equiv of 2-(lithioamino)-pyridine (Scheme 1). The N,S-acetals **2c** and **2d** underwent facile displacement with sodium methoxide in methanol to afford the corresponding N,O-acetals **4c** and **4d** in good yields. Similarly the mixed N,N-aminals **5a**,**b** and **6a**,**b** derived from 2-aminopyridine and the respective cyclic secondary amines or aniline were synthesized in good yields via direct displacement reactions on oxoketene N,S-acetals **2a**,**b** by the corresponding lithio derivatives of secondary amines or aniline (Scheme 2). The reaction provides a useful procedure for the synthesis of mixed N,N-aminals.

Our earlier attempts to cyclize **2a** with a range of oxidizing agents (K_3FeCN_6, MnO_2, HgO, LTA, etc.) did not meet with much success. However, when **2a** was refluxed with cupric chloride in THF (4 h), product analysis showed formation of only one product characterized as 2-(methylthio)-3-benzoylimidazo[1,2-*a*]pyridine **7a** on the basis of spectral and analytical data. The other substituted N,S-acetals **(2c−f)** also underwent facile ring closure under these conditions to afford 2-(methylthio)-

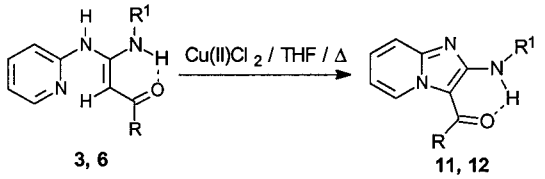
Scheme 3



10	R	Yield (%)
10a	C_6H_4	81
10c	4-ClC_6H_4	82

2,4,5	R	X	7,8,9	Yield %
2a	C_6H_5	SMe	**7a**	93
2c	4-ClC_6H_4	SMe	**7c**	93
2d	4-$MeOC_6H_4$	SMe	**7d**	91
2e	2-Furyl	SMe	**7e**	85
2f	2-Thienyl	SMe	**7f**	95
4c	4-ClC_6H_4	OMe	**8c**	71
4d	4-$MeOC_6H_4$	OMe	**8d**	87
5a	C_6H_5	N-Piperidino	**9a**	81
5b	C_6H_5	N-Morpholino	**9b**	79

Scheme 4



3,6	R	R^1	11,12	Yield %
3a	C_6H_5	2-Pyridyl	**11a**	73
3b	4-MeC_6H_4	2-Pyridyl	**11b**	75
3c	4-ClC_6H_4	2-Pyridyl	**11c**	78
3d	4-$MeOC_6H_4$	2-Pyridyl	**11d**	77
6a	C_6H_5	C_6H_5	**12a**	71
6b	C_6H_5	C_6H_5	**12b**	69

3-aroylimidazo[1,2-*a*]pyridines **7c−f** in high yields. A few of the 2-methylthio derivatives (**7a** and **7c**) were subjected to reductive dethiomethylation in the presence of Raney nickel to furnish the corresponding 2-unsubstituted-3-aroyl derivatives **10a** and **10c** in high yields. The oxidative cyclization was found to be equally facile for the corresponding N,O- and N,N-acetals derived from secondary amines to yield the corresponding 2-methoxy-**(8c**,**d)** and 2-(*N*-cycloamino)-3-aroylimidazo[1,2-*a*]pyridines **(9a**,**b)** (Scheme 3). The N,N-acetals (**3a−d, 6a**,**b**) derived from primary amines also underwent smooth cyclization under the identical conditions without formation of any side products yielding the respective 2-(2-pyridylamino)- **(11a−d)** or 2-anilino- **(12a**,**b)** 3-aroylimidazo[1,2-*a*]pyridines in 69−78% overall yields (Scheme 4). Interestingly, 3-aroyl-2-(2-pyridylamino)imidazo[1,2-*a*]pyridines **11a−c** underwent facile cyclodehydration in the presence of boron trifluoride etherate to give novel tetracyclic heteroaromatic salts **13a−c** in which positive charge is delocalized over two bridgehead nitrogen atoms. Such compounds are potential DNA intercalators.[27]

The possible mechanism for the formation of imidazo-[1,2-*a*]pyridines from N,S-, N,O-, or N,N-acetals is depicted in Scheme 6. Cupric chloride induced oxidative

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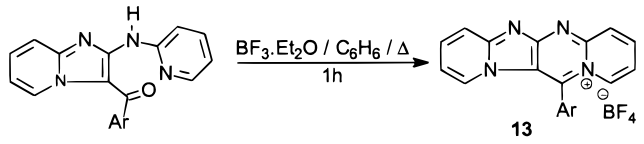
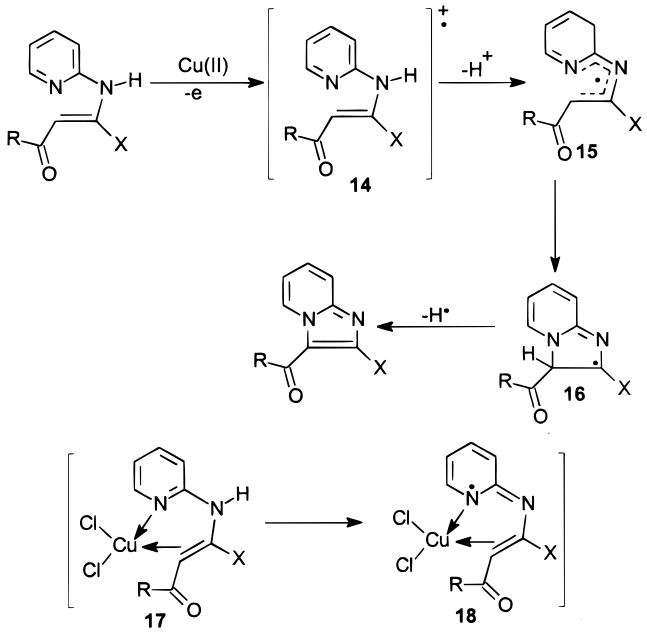
Scheme 5



11,13	Ar	Yield %
11a,13a	C_6H_5	88
11b,13b	4-MeC_6H_4	86
11c,13c	4-ClC_6H_4	86

Scheme 6



abstraction of hydrogen via cation radical intermediate **14** may give resonance stabilized aminyl radical **15** which undergoes facile intramolecular addition to the enamine double bond followed by abstraction of a hydrogen radical or proton to give the final product. Alternatively, electron transfer from nitrogen to Cu(II) ion may take place in the coordination sphere of initially formed copper complex of type **17** to give metal-complexed aminyl radical intermediate **18**[28] which on subsequent intramolecular cyclization may afford imidazo[1,2-*a*]pyridines (Scheme 6). Cuprous and cupric salts in the presence of oxygen and pyridine or amines are known to act as useful oxidizing systems for cleavage of hydrazides,[29] bishydrazone,[30] *o*-phenylenediamine,[31] and for dimerization of aromatic amines.[32] We are further exploring the mechanism of this novel oxidative cyclization with $CuCl_2$ and its application for construction of other fused heterocycles.

In summary, an efficient method for the synthesis of biologically important 2,3-functionalized imidazo[1,2-*a*]-pyridines has been described via an unprecedented $CuCl_2$-induced oxidative ring closure of novel α-oxoketene N,S-, N,O-, and N,N-acetal intermediates. The methodology allows regiospecific introduction of alkylthio, alkoxy, primary, and secondary amino group in the 2-position of imidazopyridine ring. These functionalities can be further elaborated to construct novel fused heterocyclic ring systems. The other advantages include mild reaction conditions and easy accessibility of N,S-, N,O-, and N,N-acetals, which can be prepared with large structural variations from various aminoheterocycles, thus broadening the scope of this methodology for the synthesis of diverse class of bridgehead nitrogen heterocycles.

Experimental Section

General. *n*-Butyllithium (2.5 M in hexane) was purchased from Aldrich Chemical Co. Cu(II)Cl_2 (AR grade, moisture free) and $BF_3{\cdot}Et_2O$ were purchased from E-Merck India. Benzene (AR grade) was purchased from Glaxo and used directly. Tetrahydrofuran (THF) was distilled twice over sodium/benzophenone and stored on sodium wire before use. Unless otherwise stated all reagents were purchased from local commercial sources and used without purification.

All the α-oxoketene N,S- (**2a**−**f**) and N,N- (**3a**−**d**) acetals were prepared according to our reported[26] procedure by reacting 2-(lithioamino)pyridine with corresponding α-oxoketenedithioacetals.

1-(4-Methylphenyl)-3,3-bis-(2-pyridylamino)prop-2-en-1-one (3b): light yellow crystals; mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.79−6.82 (m, 1H), 6.88−6.93 (m, 2H), 7.01 (d, 1H, J = 8.0 Hz), 7.17 (s, 1H), 7.20 (d, 2H, J = 8.4 Hz), 7.50−7.58 (m, 2H), 7.85 (d, 2H, J = 8.4 Hz), 8.12−8.13 (m, 1H), 8.38−8.40 (m, 1H), 12.98 (brs, 1H), 14.59 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 80.4, 113.5, 114.8, 117.0, 118.2, 126.6, 128.5, 137.3, 137.6, 138.1, 140.4, 145.4, 148.0, 151.9, 154.1, 155.4, 180.6; IR (KBr) 3450, 1640, 1600, 1585, 1545 cm^{-1}; MS *m*/*z* (%) 330 (M^+, 56). Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.96; H, 5.28; N, 16. 85.

1-(4-Chlorophenyl)-3,3-bis-(2-pyridylamino)prop-2-en-1-one (3c): yellow crystals; mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95−6.98 (m, 1H), 7.01−7.06 (m, 2H), 7.13 (s, 1H), 7.14 (d, 1H, J = 8.2 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.66−7.73 (m, 2H), 7.85 (d, 2H, J = 8.0 Hz), 8.25 (d, 1H, J = 4.8 Hz), 8.48 (d, 1H, J = 4.4 Hz), 13.12 (brs, 1H), 14.54 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 80.7, 114.3, 115.6, 117.7, 119.0, 128.4, 136.5, 137.9, 138.8, 139.2, 145.9, 148.6, 152.2, 154.6, 156.4, 185.8; IR (KBr) 3400, 1655, 1610, 1580, 1540 cm^{-1}; MS *m*/*z* (%) 350 (M^+, 60). Anal. Calcd for $C_{19}H_{15}ClN_4O$: C, 65.05; H, 4.31, N, 15.97. Found: C, 65.25; H, 4.21; N, 15.67.

General Procedure for the Preparation of N,O-Acetals (4c,d). To a stirred solution of methanolic sodium methoxide (prepared from 0.46 g of Na metal in 15 mL of dry methanol, 15 mmol) was added the respective N,S-acetal (10 mmol) dissolved in 15 mL of dry methanol, and the reaction mixture was stirred at room temperature for 10 min, followed by refluxing for 2 h. It was cooled to room temperature, quenched with saturated NH_4Cl solution, and extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to give the crude N,O-acetals, which were purified by column chromatrography over silica gel using hexane/ethyl acetate (9:1) as eluent.

1-(4-Chlorophenyl)-3-methoxy-3-(2-pyridylamino)prop-2-en-1-one (4c): light yellow crystals; mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.60 (s, 1H), 6.90 (m,1H), 7.40 (d, 2H, J = 9.0 Hz), 7.50−7.75 (m, 2H), 7.95 (d, 2H, J = 9.0 Hz), 8.35 (dd, 1H, J = 6.9, 1.8 Hz), 14.56 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 46.5, 90.6, 114.5, 118.5, 128.5, 128.6, 137.3, 138.0, 138.4, 146.0, 152.2, 166.6, 184.5; IR (KBr) 3417, 1617, 1589, 1213; MS *m*/*z* (%): 288 (M^+, 80); Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.53; N, 9.70. Found: C, 62.45; H, 4.42; N 9.61.

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3-Methoxy-1-(4-methoxyphenyl)-3-(2-pyridylamino)prop-2-en-1-one (4d): light yellow crystals; mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.91 (s, 3H), 5.30 (s, 1H), 6.70 (m, 1H,), 7.10−7.50 (m, 4H), 7.80−8.15 (m, 3H,), 8.35 (dd, 1H, J = 6.9, 1.5 Hz), 14.0 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 46.4, 55.8, 87.6, 113.8, 113.9, 119.8, 129.0, 130.6, 131.0, 138.2, 147.8, 151.2, 162.0, 193.1; IR(KBr) 3458, 1627, 1599, 1339 cm^{-1}; MS *m*/*z* (%) 284 (M$^+$, 100). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.65; H, 5.60; N, 11.12.

General Procedure for the Preparation of Mixed N,N-Aminals (5a,b, 6a,b). To a stirred solution of aniline (0.91 mL, 10 mmol) in dry THF (20 mL) was added *n*-butyllithium (15 mmol) under nitrogen atmosphere, over a period of 20 min at room temperature (25 °C). The reaction mixture was stirred for 30 min at the same temperature, and the lithiation was indicated by the appearance of reddish brown color. A solution of N,S-acetal (10 mmol) in dry THF (25 mL) was added, and the reaction mixture was refluxed for 4 h. It was then brought to room temperature, poured into saturated aq NH_4Cl solution, and extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to give crude products which were purified by passing through a silica gel column using ethyl acetate/hexane (1:9) as eluent.

1-Phenyl-3-(1-piperidino)-3-(2-pyridylamino)prop-2-en-1-one (5a): yellow crystals; mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.60 (m, 2H), 1.73−1.79 (m, 4H), 3.05 (t, 4H, J = 4.0 Hz), 5.45 (s, 1H), 7.01−7.03 (m, 1H), 7.13 (d, 1H, J = 7.8 Hz), 7.35−7.39 (m, 3H), 7.41−7.45 (m, 1H), 7.77−7.81 (m, 2H), 8.40−8.44 (m, 1H), 12.71 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 23.8, 26.8, 55.1, 83.2, 115.0, 119.5, 127.8, 128.2, 130.4, 137.5, 140.8, 147.8, 153.4, 160.1, 189.0; IR (KBr) 3405, 1605, 1560, 1490 cm^{-1}; MS *m*/*z* (%) 307 (M$^+$, 80). Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.88; N, 13.67. Found: C, 74.45; H, 6.68; N, 13.88.

3-(4-Morpholino)-1-phenyl-3-(2-pyridylamino)prop-2-en-1-one (5b): light yellow crystals; mp 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36−3.38 (m, 4H), 3.80−3.81(m, 4H), 5.56 (s, 1H), 6.91−6.94 (m, 1H,), 7.10 (d, 1H, J = 8.0 Hz), 7.40−7.46 (m, 3H), 7.60−7.63 (m, 1H), 7.81−7.87 (m, 2H), 8.31−8.33 (m, 1H), 12.62 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 48.6, 66.1, 82.5, 114.0, 118.2, 127.0, 128.2, 130.4, 138.0, 141.0, 148.5, 153.8, 160.6, 188.3; IR (KBr) 3451, 1619, 1536, 1521, 1490 cm^{-1}; HRMS *m*/*z* M$^+$ calcd for $C_{18}H_{19}O_2N_3$ 309.147, found 309.146. Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.97; H, 5.95; N, 13.75.

3-Anilino-1-phenyl-3-(2-pyridylamino)prop-2-en-1-one (6a): colorless crystals; mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H), 6.92−6.95 (m, 1H), 7.03 (d, 1H, J = 8.5 Hz), 7.25−7.39 (m, 7H), 7.43−7.46 (m, 2H), 7.67 (dd, 1H, J = 7.3, 1.5 Hz), 7.74 (dd, 1H, J = 4.8, 1.2 Hz), 8.19 (d, 1H, J = 5.4 Hz), 12.19 (brs, 1H), 13.36 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 78.1, 114.2, 117.5, 125.7, 126.3, 126.7, 128.1, 129.5, 130.2, 137.4, 138.6, 141.0, 145.9, 154.8, 159.2, 185.7; IR (KBr) 3410, 1658, 1550, 1458 cm^{-1}; MS *m*/*z* (%) 315 (M$^+$, 58). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17, H, 5.43; N, 13.32. Found: C, 76.33; H, 5.21; N, 13.88.

3-Anilino-1-(4-methylphenyl)-3-(2-pyridylamino)prop-2-en-1-one (6b): yellow crystals; mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 5.66 (s, 1H), 6.90−6.96 (m, 1H), 7.02 (d, 1H, J = 8.4 Hz), 7.14 (d, 2H, J = 7.5 Hz), 7.25−7.29 (m, 1H), 7.37 (d, 2H, J = 8.0 Hz), 7.41−7.45 (m, 2H), 7.64−7.66 (m, 3H), 8.18 (d, 1H, J = 8.0 Hz), 12.16 (brs, 1H), 13.13 (brs, 1H); ^{13}C NMR ($CDCl_3$) 21.3, 114.06, 117.4, 125.6, 126.1, 126.6, 128.8, 129.4, 137.4, 138.1, 138.5, 140.4, 145.9, 154.8, 159.0, 185.9; IR (KBr) 3400, 1654, 1554, 1448, 1404 cm^{-1}; MS *m*/*z* (%): 329 (M$^+$, 65). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.75. Found: C, 76.44; H, 5.69; N, 12.58.

General Procedure for Oxidative Cyclization of N,S-, N,N-, and N,O- Acetals to Imidazo[1,2-*a*]pyridines. To a stirred solution of respective N,S-, N,O-, or N,N-acetal (10 mmol) in dry tetrahydrofuran (30 mL) was added anhydrous Cu(II)Cl_2 (2.02 g, 15 mmol), and the reaction mixture was refluxed with stirring for 3−4 h (monitored by TLC). The initial pale green color of the reaction mixture faded away, and after 3 h it gradually turned reddish brown. The reaction mixture after cooling was poured into water and filtered to remove insoluble impurities. The filtrate was extracted with chloroform, and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to give crude viscous residue which was passed through silica gel column using hexane/ethyl acetate (9:1) as eluent, to afford pure imidazo[1,2-*a*]pyridines in high yields. The analytical and spectral data for the purified compounds are reported below:

3-Benzoyl-2-(methylthio)imidazo[1,2-*a*]pyridine (7a): colorless crystals; mp 140−141 °C, lit.[19a] mp 139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 6.99 (ddd, 1H, J = 6.9, 6.6, 0.9 Hz), 7.45 (dd, 1H, J = 6.9, 0.9 Hz), 7.48−7.51 (m, 3H), 7.53−7.60 (m, 2H), 7.66 (dt, 1H, J = 9.0, 0.9 Hz), 9.52 (dt, 1H, J = 6.6, 0.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8, 114.1, 115.7, 120.2, 128.2, 128.5, 128.6, 129.6, 131.5, 139.8, 148.0, 154.0, 185.5; IR (KBr) 1627, 1590, 1224; MS *m*/*z* (%) 268 (M$^+$, 25.3), 267 (M$^+$ − 1, 100). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.34; H, 4.45; N, 10.55.

3-(4-Chlorobenzoyl)-2-(methylthio)imidazo[1,2-*a*]pyridine (7c): colorless crystals; mp 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 7.05 (ddd, 1H, J = 9.6, 6.9, 1.1 Hz), 7.47 (ddd, 1H, J = 9.6, 6.9, 1.1 Hz), 7.50 (d, 2H, J = 9.0 Hz), 7.61 (d, 2H, J = 9.0 Hz), 7.66 (dt, 1H, J = 9.6, 1.1 Hz), 9.53 (dt, 1H, J = 6.6, 1.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8, 114.4, 115.8, 119.8, 128.6, 129.0, 129.7, 129.9, 137.9, 138.1, 148.1, 156.1, 184.1; IR (KBr) 1670, 1627, 1599, 1221; MS *m*/*z* (%) 303 (M$^+$, 100), 288 (M$^+$ − 15, 14.40), 270 (M$^+$ − 33, 51). Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 59.5; H, 3.62; N, 9.21. Found: C, 59.63; H, 3.55; N, 9.33.

3-(4-Methoxybenzoyl)-2-(methylthio)imidazo[1,2-*a*]pyridine (7d): colorless crystals; mp 141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.88 (s, 3H), 6.98 (ddd, 1H, J = 6.8, 6.5, 0.9 Hz), 7.01 (d, 2H, J = 9.0 Hz), 7.44 (ddd, 1H, J = 9.6, 6.8, 0.9 Hz), 7.62 (dt, 1H, J = 9.6, 0.9 Hz), 7.70 (d, 2H, J = 9.0 Hz), 9.41 (dt, 1H, J = 6.5, 0.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.0, 55.4, 113.8, 113.9, 115.8, 120.4, 128.3, 129.2, 130.8, 132.4, 147.8, 154.5, 162.8, 184.7; IR (KBr) 1670, 1604, 1339, 1222 cm-^{1}; MS *m*/*z* (%) 298 (M$^+$, 19.7), 297 (M$^+$ − 1, 100). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.60; N, 9.39. Found: C, 64.60; H, 4.45; N, 9.48.

3-(2-Furoyl)-2-(methylthio)imidazo[1,2-*a*]pyridine (7e): colorless crystals; mp 141−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (s, 3H), 6.60 (dd, 1H, J = 4.0, 2.0 Hz), 6.98 (ddd, 1H, J = 6.9, 6.7, 1.1 Hz), 7.32 (d, 1H, J = 4.0 Hz), 7.44 (ddd, 1H, J = 9.6, 6.9, 1.1 Hz), 7.62 (dt, 1H, J = 9.6, 1.1 Hz), 7.69 (d, 1H, J = 3.0 Hz), 9.26 (dt, 1H, J = 6.7, 1.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.0, 112.2, 114.1, 115.9, 118.2, 120.2, 128.1, 129.3, 146.2, 147.9, 151.6, 154.0, 171.9; IR (KBr) 1687, 1627, 1606, 1232 cm^{-1}; MS *m*/*z* (%) 258 (M$^+$, 100), 243 (M$^+$ − 15, 21.8). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.84. Found: C, 60.56; H, 3.73; N, 10.90.

2-(Methylthio)-3-(2-thienoyl)imidazo[1,2-*a*]pyridine (7f): light yellow crystals; mp 152−153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3H), 6.98 (ddd, 1H, J = 6.9, 6.7, 1.1 Hz), 7.15 (dd, 1H, J = 4.9, 3.8 Hz), 7.45 (ddd, 1H, J = 9.2, 6.9, 1.1 Hz), 7.63 (dt, 1H, J = 9.2, 1.2 Hz), 7.70 (dd, 1H, J = 4.3, 1.2 Hz), 7.77 (dd, 1H, J = 4.3, 1.2 Hz), 9.29 (dt, 1H, J = 6.9, 1.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 114.1, 115.8, 120.4, 127.4, 128.2, 129.3, 132.7, 133.0, 142.8, 147.9, 154.2, 177.4; IR (KBr) 1670, 1649, 1583, 1236 cm^{-1}; MS *m*/*z* (%) 274 (M$^+$, 100), 259 (M$^+$ − 15, 13.9), 241 (M$^+$ − 33, 84.4). Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 56.80; H, 3.75; N, 11.65.

3-(4-Chlorobenzoyl)-2-methoxyimidazo[1,2-*a*]pyridine (8c): yellow crystals; mp 156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.04 (ddd, 1H, J = 6.9, 6.6, 1.1 Hz), 7.39 (d, 2H, J = 9.0 Hz), 7.45−7.54 (m, 2H), 7.65 (d, 2H, J = 9.0 Hz), 9.68 (dt, 1H, J = 6.6, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 114.1, 115.4, 127.7, 129.0, 129.5, 130.0, 137.2, 137.9, 144.8, 163.3, 182.4; IR (KBr) 1600, 1559, 1402, 1226 cm^{-1}; MS *m*/*z* (%) 286 (M$^+$, 100). Anal. Calcd for $C_{15}H_{11}N_2O_2Cl$: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.78; H, 3.79; N, 9.95.

2-Methoxy-3-(4-methoxybenzoyl)imidazo[1,2-*a*]pyridine (8d): white crystals; mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.01 (s, 3H), 6.95 (d, 2H, J = 8.1 Hz), 7.04 (t, 1H, J = 6.0 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.4 Hz), 9.65 (d, 1H, J = 6.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.3, 56.1, 112.9, 113.0, 114.1, 115.4, 128.9, 129.3, 131.0, 132.0, 144.7, 162.3, 162.9, 183.2; IR (KBr) 1605, 1556, 1406 cm^{-1}; MS *m*/*z* (%) 282 (M$^+$, 100). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.25; H, 4.89; N, 10.01.

3-Benzoyl-2-(1-piperidino)imidazo[1,2-*a*]pyridine (9a): yellow crystals; mp 134−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14−1.18 (m, 4H), 1.33−1.38 (m, 2H), 3.11−3.13 (m, 4H), 6.92−6.94 (m, 1H) 7.40−7.46 (m, 3H), 7.49−7.52 (m, 2H), 7.78(d, 2H, J = 7.5 Hz), 9.58 (d, 1H, J = 5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 24.9, 52.6, 109.7, 113.2, 114.9, 128.1, 128.3, 128.9, 129.4, 131.4, 139.9, 146.3, 161.8, 185.0; IR (KBr) 1630, 1585, 1539 cm^{-1}; HRMS *m/z* M^+ calcd for $C_{19}H_{19}N_3O$ 305.152, found 305.1519. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.79; H, 6.28; N, 13.77. Found: C, 74.87; H, 6.01; N, 13.91.

3-Benzoyl-2-(4-morpholino)imidazo[1,2-*a*]pyridine (9b): yellow crystals; mp 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (t, 4H, J = 7.5 Hz), 3.31 (t, 4H, J = 7.2 Hz), 6.98 (dt, 1H, J = 7.1, 1.5 Hz), 7.45−7.49 (m, 3H), 7.53−7.56 (m, 2H), 7.80−7.82 (m, 2H), 9.59 (d, 1H, J = 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.5, 65.9, 110.0, 113.7, 115.2, 128.2, 128.5, 128.9, 129.6, 131.8, 139.6, 146.1, 160.9, 184.9; IR (KBr) 1599, 1588, 1568, 1462 cm^{-1}; HRMS *m/z* M^+ calcd for $C_{18}H_{17}N_3O_2$ 307.132, found 307.131. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.39; H, 5.58; N, 13.68. Found: C, 70.21; H,5.42; N, 13.79.

3-Benzoyl-2-(2-pyridylamino)imidazo[1,2-*a*]pyridine (11a): colorless crystals; mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85−6.92 (m, 2H), 7.26−7.56 (m, 3H), 7.61−7.69 (m, 5H), 8.16−8.19 (m, 1H), 8.20 (brs, 1H), 8.41(d, 1H, J = 8.0 Hz), 8.92 (d, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 113.0, 115.6, 118.5, 122.2, 128.0, 129.0, 129.5, 130.1, 131.1, 139.9, 140.0, 147.7, 155.7, 182.6; IR (KBr) 3350, 1585, 1540, 1490, 1465 cm^{-1}; MS *m/z* (%) 314 (M^+, 100). Anal. Calcd for $C_{19}H_{14}N_3O$: C, 72.59; H, 4.49; N, 17.82. Found: C, 72.71; H, 4.23; N, 17.94.

3-(4-Methylbenzoyl)-2-(2-pyridylamino)imidazo[1,2-*a*]-pyridine (11b): white crystals; mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 6.88 (t, 2H, J = 6.0 Hz), 7.35 (d, 2H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.8 Hz), 7.49−7.56 (m, 1H), 7.59 (d, 2H, J = 8 Hz), 7.65−7.70 (m, 1H), 8.19 (brs, 1H), 8.40 (d, 2H, J = 6.5 Hz), 8.91 (d, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 109.5, 112.9, 115.6, 118.6, 122.2, 127.3, 128.0, 129.0, 129.9, 130.0, 137.2, 140.0, 141.7, 147.6, 155.6, 182.8; IR (KBr) 3300, 1610, 1590, 1565, 1490 cm^{-1}; MS *m/z* (%) 328 (M^+, 100). Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.29; H, 4.75; N, 17.22.

3-(4-Methoxybenzoyl)-2-(2-pyridylamino)imidazo[1,2-*a*]-pyridine (11c): white crystals; mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.87 (t, 2H, J = 8 Hz), 7.03 (d, 2H, J = 7.2 Hz), 7.37−7.45 (m, 1H), 7.55(d, 2H, J = 4.0 Hz), 7.68 (d, 2H, J = 8.5 Hz), 8.18 (d, 1H, J = 3.9 Hz), 8.30 (brs, 1H), 8.42 (d, 1H, J = 8.0 Hz), 8.90 (d, 1H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 109.5, 112.0, 113.3, 114.6, 115.6, 117.3, 128.1, 129.4, 129.8, 131.8, 137.8, 146.7, 148.0, 152.6, 153.0, 162.5, 182.7; IR (KBr) 3110, 1645, 1590, 1541, 1465 cm^{-1}; MS *m/z* (%) 344 (M^+, 100). Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.85; H, 4.45; N, 16.44.

3-(4-Chlorobenzoyl)-2-(2-pyridylamino)imidazo[1,2-*a*]-pyridine (11d): yellow crystals; mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (t, 2H, J = 6.3 Hz), 7.27−7.50 (m, 1H), 7.56 (d, 2H, J = 8.5 Hz), 7.57−7.59 (m, 1H), 7.64 (d, 2H, J = 8.1 Hz), 7.69−7.72 (m, 1H), 8.21 (m, 1H), 8.33 (brs, 1H), 8.40 (d, 1H, J = 8.6 Hz), 8.83 (d, 1H, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.6, 114.4, 115.6, 117.6, 117.7, 119.9, 128.3, 136.6, 137.9, 138.7, 139.2, 145.9, 148.6, 152.2, 154.5, 156.3, 183.5; IR(KBr) 3125, 1655, 1599, 1555, 1535, 1460 cm^{-1}; MS *m/z* (%) 348 (M^+, 100). Anal. Calcd for $C_{19}H_{13}ClN_4O$: C, 65.43; H, 3.75; N, 16.06. Found: C, 65.61; H, 3.59; N, 16.21.

2-Anilino-3-benzoylimidazo[1,2-*a*]pyridine (12a): yellow crystals; mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75−6.77 (m, 1H), 6.98 (dt, 1H, J = 7.0, 1.5 Hz), 7.25−7.32 (m, 2H), 7.36−7.40 (m, 1H), 7.49−7.52 (m, 1H), 7.53−7.62 (m, 7H), 8.10 (brs, 1H), 8.52 (d, 1H, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 113.0, 115.6, 118.5, 122.2, 127.1, 128.0, 129.0, 129.5, 130.1, 131.1, 139.9, 140.0, 147.7, 155.7, 182.6; IR (KBr) 3120, 1590, 1575 cm^{-1}; MS *m/z* (%) 313 (M^+, 100). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.40. Found: C, 76.82; H, 4.92; N, 13.31.

2-Anilino-3-(4-methylbenzoyl)imidazo[1,2-*a*]pyridine (12b): yellow crystals; mp 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 6.73−6.77 (m, 1H), 6.97−7.03 (m, 1H), 7.25−7.41 (m, 5H), 7.49−7.66 (m, 5H), 8.23 (brs, 1H), 8.49 (d, 1H, J = 5.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6, 109.4, 112.9, 115.6, 118.6, 122.1, 127.3, 128.0, 129.2, 129.8, 130.0, 137.2, 140.0, 141.6, 147.5, 155.6, 182.8; IR (KBr) 3150, 1610, 1580, 1545, 1430, 1415 cm^{-1}; MS *m/z* (%) 327 (M^+, 100). Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.21; H, 5.21; N, 12.97.

General Procedure for Raney Nickel Dethiomethylation of 7 to 10. To a stirred solution of 3-aroyl-2-(methylthio)-imidazo[1,2-*a*]pyridines (**7a** or **7c**) (2.5 mmol) in ethanol (25 mL) was added Raney nickel (W2, three times by weight), and the reaction mixture was refluxed with stirring for 6 h (monitored by TLC). It was then filtered through a sintered glass funnel and washed with ethanol (10 mL), and the filtrate was evaporated under reduced pressure. The residue thus obtained was diluted with chloroform, washed with water, dried (Na_2SO_4), and evaporated to give crude products which were purified by passing through silica gel column using hexane/ethyl acetate (9:1) as eluent.

3-Benzoylimidazo[1,2-*a*]pyridine (10a): colorless crystals; mp 135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (ddd, 1H, J = 6.9, 6.6, 1.0 Hz), 7.50−7.60 (m, 4H), 7.70 (m, 2H), 7.79 (dt, 1H, J = 8.8, 1.1 Hz), 8.21 (s, 1H), 9.74 (dt, 1H, J = 6.6, 0.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 115.1, 117.7, 123.5, 128.5, 128.8, 129.4, 130.2, 132.0, 138.4, 139.2, 145.6, 189.7; IR (KBr) 1689, 1597, 1223 cm^{-1}; MS *m/z* (%) 222 (M^+, 100). Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.53; N, 12.60. Found: C, 75.70; H, 4.35; N, 12.50.

3-(4-Chlorobenzoyl)imidazo[1,2-*a*]pyridine (10c): colorless crystals; mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08−7.20 (m, 1H), 7.40−7.50 (m, 1H), 7.54 (d, 2H, J = 8.0 Hz), 7.86 (d, 2H, J = 8.4 Hz), 8.06−8.21 (m, 1H), 8.53 (s, 1H), 9.71−9.86 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 115.3, 117.8, 128.9, 129.5, 130.2, 130.3, 132.0, 137.6, 138.4, 145.6, 183.4; IR (KBr) 1650, 1585, 1500, 1470 cm^{-1}; MS *m/z* (%) 256 (M^+, 32), 222 (M^+ − 34, 100). Anal. Calcd for $C_{14}H_9ClN_2O$: C, 66.51; H, 3.53; N, 10.91. Found: C, 66.69; H, 3.45; N, 10.82.

General Procedure for BF_3·Et_2O-Assisted Cyclization of 11a−c To Give Salts 13a−c. To a solution of **11** (10 mmol) in dry benzene (30 mL) was added boron trifluoride etherate (3 mL), and the reaction mixture was refluxed with stirring for 1 h. On cooling, the yellow crystalline salt that separated was filtered and washed with benzene and further purified by crystallization from glacial acetic acid.

13a: yellow crystals; mp 219−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (d, 1H, J = 7.2 Hz), 7.41−7.42 (m, 1H), 7.51−7.53 (m, 1H), 7.75−8.00 (m, 5H), 8.11−8.22 (m, 2H), 8.34−8.45 (m, 2H), 8.56 (d, 1H, J = 6.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.7, 118.0, 119.8, 120.2, 124.9, 126.7, 128.8, 129.2, 129.7, 131.8, 133.3, 137.9, 140.3, 140.8, 148.2, 158.9, 159.2; IR(KBr) 1650, 1580, 1521, 1460, 1060 cm^{-1}; FAB MS *m/z* (%) 297 (M^+ − BF_4, 100). Anal. Calcd for $C_{19}H_{13}N_4BF_4$: C, 59.41; H, 3.41, N, 14.59. Found: C, 59.67; H, 3.31; N, 14.66.

13b: yellow crystals; mp 234−235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H), 7.33 (t, 1H, J = 6.3 Hz), 7.51 (d, 1H, J = 6.0 Hz), 7.72−7.75 (m, 3H), 7.78 (d, 2H, J = 8.2 Hz), 8.14 (d, 1H, J = 8.1 Hz), 8.20−8.23 (m, 1H), 8.37 (m, 1H), 8.45 (d, 1H, J = 8.4 Hz), 8.56 (d, 1H, J = 8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.4, 115.7, 118.0, 119.6, 120.2, 121.9, 126.6, 129.0, 129.7, 131.7, 132.0, 137.9, 140.6, 140.7, 143.3, 148.1, 158.7, 159.0; IR (KBr) 1584, 1519, 1510, 1468, 1065; FAB MS *m/z* (%) 311 (M^+ − BF_4, 100). Anal. Calcd for $C_{20}H_{15}N_4BF_4$: C, 60.33; H, 3.80; N, 14.07. Found: C, 60.51; H, 3.65; N, 14.22.

13c: yellow crystals; mp 239−240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (t, 1H, J = 5.4 Hz), 7.53 (dt, 1H, J = 6.8, 1.2 Hz), 7.75 (d, 2H, J = 8.4 Hz), 7.82 (d, 2H, J = 8.5 Hz), 7.92−8.05 (m, 1H), 8.17−8.28 (m, 1H), 8.35 (t, 1H, J = 7.8 Hz), 8.44−8.45 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 114.7, 117.0, 119.1, 121.2, 124.5, 124.7, 128.6, 128.2, 128.7, 130.5, 132.3, 136.9, 141.3, 141.8, 149.2, 158.5, 159.2; IR(KBr) 1670, 1540, 1521, 1460, 1065 cm^{-1}; FAB MS *m/z* (%) 331 (M^+ − BF_4, 100). Anal. Calcd for $C_{19}H_{12}ClN_4BF_4$: C, 54.52; H, 2.89, N, 13.38. Found: C, 54.75; H, 2.71; N, 13.56.

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