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$CuSO_4$–Glucose for in Situ Generation of Controlled Cu(I)–Cu(II) Bicatalysts: Multicomponent Reaction of Heterocyclic Azine and Aldehyde with Alkyne, and Cycloisomerization toward Synthesis of N-Fused Imidazoles

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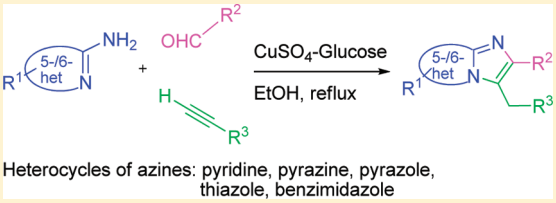
Supporting Information

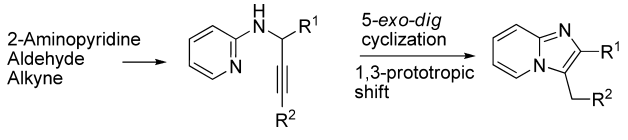
ABSTRACT: The catalytic efficiency of mixed Cu(I)–Cu(II) system in situ generated by partial reduction of $CuSO_4$ with glucose in ethanol (nonanhydrous) under open air has been explored. With this catalysis, the multicomponent cascade reaction of A^3-coupling of heterocyclic amidine with aldehyde and alkyne, 5-*exo-dig* cycloisomerization, and prototropic shift has afforded an efficient and eco-friendly synthesis of therapeutically important versatile N-fused imidazoles. Diverse heterocyclic amidines, several of which are known to be poorly reactive, and aldehydes are compatible in this catalytic process.



The multicomponent reaction of aldehyde with amine and alkyne (A^3-coupling) toward synthesis of propargyl amine has gained importance in organic synthesis.[1] Its incorporation in cascade processes of tethered cyclization with activation of triple bond in propargyl amine affords access to versatile molecular complex compounds.[2] In these reaction sequences, the group 11 metal (Cu, Ag, and Au) salts offer efficient catalysis for alkyne C–H activation in alkynylation with σ-activated imine and π-activation of triple bond toward cyclization. The synthesis of many novel scaffolds/motifs have been successfully accomplished with the use of a mixture of catalytic species that are chemically compatible, such as mixed copper salts [CuCl–Cu(OTf)$_2$],[3] Cu(I)–Au(III) system,[4] and CuBr–Wilkinson's catalyst.[5] Recently, a strategic use of this approach with CuCl–Cu(OTf)$_2$ catalysis[6] has been documented for the multicomponent synthesis of imidazo[1,2-*a*]pyridine,[7] a medicinally important scaffold, from 2-aminopyridine (a less reactive amine), aldehyde, and alkyne (Scheme 1). Several drugs such as zolpidem, necopidem, and saripidem are accessible by this one-pot synthesis.[6]

For this cascade reaction, the subsequent modifications on catalysis such as Cu(I)–*p*-TsOH,[8a] Cu(I)–$NaHSO_4$–SiO_2,[8b] CuCl–$ZnCl_2$,[8c] and $InBr_3$ under basic conditions[8d] have been reported. However, these methods suffer from the requirements of a stringent anaerobic procedure and harsh conditions and limited substrate scope.

Scheme 1. Approach of Cascade A^3-Coupling–Cyclization–Prototropic Shift toward Synthesis of Imidazopyridine



The Cu(I)-catalyst in situ generated from Cu(II) and reducing agents especially sodium ascorbate in water provides excellent results for the modified Huisgen cycloaddition[9,10] of alkyne with azide to form triazole, the most efficient click chemical reaction.[11] The reduction of Cu(II) with reducing sugar to Cu_2O is used for the estimation of reducing sugar (especially glucose) in analytical and clinical chemistry (Fehling's and Benedict's tests). However, there is no report for in situ generation and use of reduced metal [Cu(I)] as catalyst in A^3-coupling and its cascade process. We speculated that Cu(I) in situ generated by reduction of $CuSO_4$ with reducing carbohydrates can be an efficient catalyst in A^3-coupling and cascade cycloisomerization toward synthesis of imidazopyridine. Moreover, unlike reported procedures, this approach could possibly facilitate the use of environment-friendly solvent, avoidance of handling difficulty/hazards and or costly σ/π-Lewis acid as catalyst, nonrequirement of anhydrous conditions, and the reaction for versatile heterocyclic amidines as well as other coupling components. It is noteworthy that like imidazo[1,2-*a*]pyridine, other N-fused imidazoles[12,13] and their derivatives[14] are also therapeutically important, yet their syntheses were not explored in reported methodologies. Here, we report a mixed Cu(I)–Cu(II) system in situ generated from partial reduction of $CuSO_4$ with glucose in ethanol (nonanhydrous) under open air, that efficiently catalyzes the cascade reaction of A^3-coupling–cycloisomeriza-

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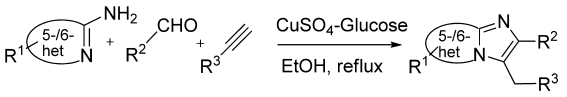
tion toward environment-friendly access to N-fused imidazoles. In this catalytic process, various heterocyclic amidines, several of which are poorly reactive amines, aldehydes, and alkynes afforded versatile N-fused imidazoles in good to high yields (Scheme 2).

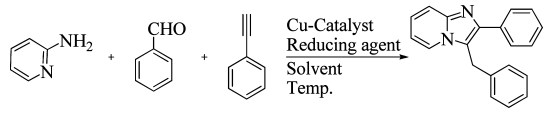
Scheme 2. Cu(I)−Cu(II) Catalysis in A^3-Coupling and Cascade Cycloisomerization: Synthesis of Versatile N-Fused Imidazoles



Heterocycles of azines: pyridine, pyrazine, pyrazole, thiazole, benzimidazole

Our investigation centered on in situ generation of Cu(I) by reduction of Cu(II) salt with reducing carbohydrates and its function as π- and σ-electrophilic Lewis acid in cascade A^3-coupling and 5-*exo*-*dig* cycloisomerization. Accordingly, we evaluated the efficiency of Cu(II) salts, reducing agents, solvents, and conditions. 2-Aminopyridine, benzaldehyde, and phenylacetylene were chosen as model substrates. The results are summarized in Table 1. Initial experiments for the survey of Cu(II) salts ($CuSO_4$, $Cu(OAc)_2$, $CuCl_2$, and $Cu(NO_3)_2$), reducing agents (sodium ascorbate, D-glucose, trisodium citrate, lactose), and solvents (H_2O, EtOH, PEG-400, toluene, EtOH−H_2O, PEG-400−H_2O, toluene−H_2O) revealed $CuSO_4$−glucose−EtOH to be most effective. The superior efficiency of $CuSO_4$−glucose−ethanol impelled us to investigate isopropoanol as both reducing agent and solvent in place of glucose−ethanol. However, it resulted in inferior yield of product (data not shown in table). Use of water as solvent or its mixture with other solvents (Table 1, entries 2 and 4−6) promoted the oxidative dimerization of alkyne more. This might be plausibly due to enhanced oxidation potential of Cu(II) in these solvents. On the other hand, the presence of Cu(II) was found to be necessary. The reaction conditions that can promote enhanced formation of Cu(I) with reduced possibility of regenerating back to Cu(II), such as the use of higher quantity of glucose or anhydrous deoxygenated EtOH under nitrogen, resulted in inferior yields of product (Table 1, entries 13−16). The presence of Cu(II) in optimized conditions under open air was confirmed by treating the reaction mixture with aqueous ammonia or potassium ferrocyanide solutions, which generated blue color or red precipitates, respectively. These indicate that this A^3-coupling−cycloisomerization cascade requires the crucial optimum conditions, which can provide controlled partial reduction of Cu(II) to Cu(I) toward in situ generation of mixed Cu(I)−Cu(II) catalysts system, but does not induce oxidation to susceptible reactant such as alkyne by Cu(II). Increasing the temperature from 80 to 100 °C enhanced the yield (Table 1, entry 13 vs 15). Variation in equivalence revealed that $CuSO_4$ (15 mol %)−glucose (30 mol %) (Table 1, entries 8 and 14 vs 13) was best. The reactions catalyzed by commercially received CuCl, $CuSO_4$, or CuCl−$CuSO_4$ (Table 1, entries 17−19) provided inferior results. These reveal the superior catalytic efficiency of the mixed Cu(I)−Cu(II) system in situ generated from $CuSO_4$−glucose in EtOH under open air for this cascade reaction. The experimental procedure is simple and straightforward.

Table 1. Evaluation of Cu(II)-Reducing Agents and Conditions[a]



entry	Cu-catalyst (mol %)	reducing agent (mol %)	solvent	temp (°C)[b]	yield (%)[c]
1	$CuSO_4·5H_2O$ (5)	Na-ascorbate (10)	EtOH	80	37
2	$CuSO_4·5H_2O$ (5)	Na-ascorbate (10)	H_2O	80	17
3	$CuSO_4·5H_2O$ (5)	Na-ascorbate (10)	toluene	80	20
4	$CuSO_4·5H_2O$ (5)	Na-ascorbate (10)	EtOH−H_2O	80	22
5	$CuSO_4·5H_2O$ (5)	Na-ascorbate (10)	toluene−H_2O	80	NR[d]
6	$CuSO_4·5H_2O$ (5)	Na-ascorbate (10)	PEG−H_2O	80	15
7	$CuSO_4·5H_2O$ (10)	lactose (20)	EtOH	80	32
8	$CuSO_4·5H_2O$ (10)	glucose (20)	EtOH	80	50
9	$CuSO_4·5H_2O$ (10)	trisod. citrate (20)	EtOH	80	35
10	$Cu(OAc)_2·H_2O$ (10)	glucose (20)	EtOH	80	43
11	$Cu(NO_3)_2·3H_2O$ (10)	glucose (20)	EtOH	80	12
12	$CuCI_2$ (10)	glucose (20)	EtOH	80	17
13	$CuSO_4·5H_2O$ (15)	glucose (30)	EtOH	80	56
14	$CuSO_4·5H_2O$ (10)	glucose (30)	EtOH	80	26
15	$CuSO_4·5H_2O$ (15)	glucose (30)	EtOH	100	79
16[e]	$CuSO_4·5H_2O$ (15)	glucose (30)	EtOH	100	68
17	CuCI (15)	glucose (30)	EtOH	100	56
18	$CuSO_4·5H_2O$ (15)		EtOH	100	12
19	CuCI(15) and $CuSO_4·5H_2O$ (5)		EtOH	100	63

[a]Reactants (mmol): 2-aminopyridine (1 mmol), benzaldehyde (1 mmol), phenylacetylene (1.5 mmol). Solvents were used as commercially received without further distillation. [b]Silicon oil bath temperature. [c]Isolated yields. [d]No Reaction. [e]Reaction was carried out using anhydrous deoxygenated EtOH under N_2.

With the optimized multicomponent protocol in hand, we next set out to explore its scope. To our delight, versatile heterocyclic amidines including 2-aminopyridine, 2-aminopyrazine, 2-aminopyrazole, 2-aminothiazole, and 2-aminobenzimidazole underwent smooth reactions (Table 2). This generalization of the present method is particularly interesting because the heterocyclic amidines other than 2-aminopyridine are known to be poorly reactive azines in multicomponent reactions,[13d,e,15] were not explored previously in this type of cascade methodologies, and provide therapeutically important compounds. Various aromatic aldehydes and alkynes afforded good to high yields of products. However, aliphatic aldehydes provided less yields because of fewer conversions, and aliphatic alkynes (octyne and hexyne) resulted in formation of complex mixture of products. Both electron-withdrawing and donating functionalities on aldehydes were equally compatible.

The tolerance of functionalities such as chloro, bromo, nitro, methoxy, and cyano in this protocol provides the opportunity of their various further chemical manipulations in products. Several therapeutically relevant moieties could be incorporated at ease by this method into N-fused imidazoles.

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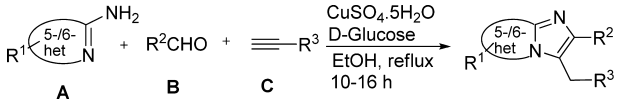
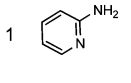
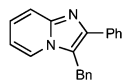
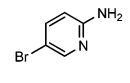
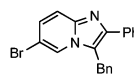
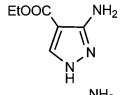
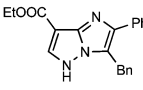
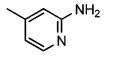
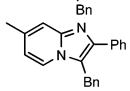
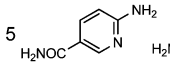
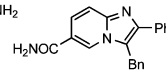
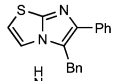
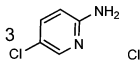
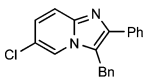
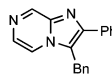
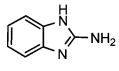
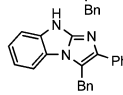
Table 2. Synthesis of Versatile N-Fused Imidazoles[a]



Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
Variation in heterocyclic amidine for the reaction with benzaldehyde and phenylacetylene											
1			79	4			80	7			45
2			74	5			76	8			46
3			79	6			73	9			63
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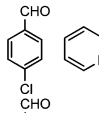
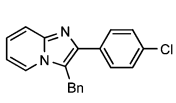
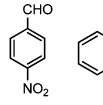
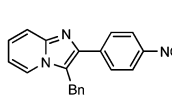
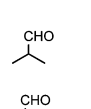
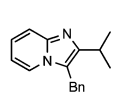
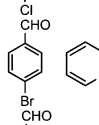
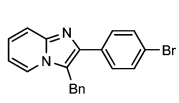
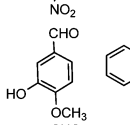
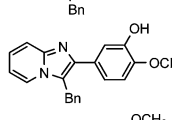
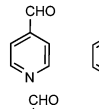
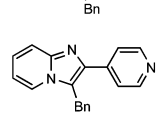
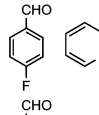
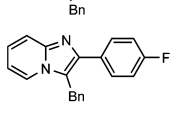
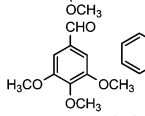
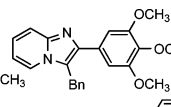
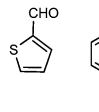
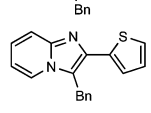
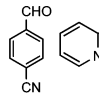
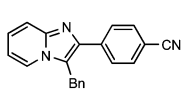
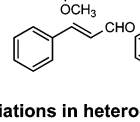
10			73	14			73	18[c]			20
11			71	15			80	19			70
12			72	16			77	20			66
13			82	17			70				
Variations in heterocyclic amidine, aldehyde, and alkyne											
21			72	22			69	23			71
24			78								

[a]Reaction conditions: A (1 mmol), B (1 mmol), C (1 mmol), $CuSO_4 \cdot 5H_2O$ (15 mol %), D-glucose (30 mol %). [b]Isolated yields. [c]Isobutyraldehyde (1.5 mmol).

In conclusion, we have explored catalytic efficiency of mixed Cu(I)−Cu(II) system in situ generated by partial reduction of $CuSO_4$ with glucose in ethanol (nonanhydrous) under open air for the multicomponent reaction of heterocyclic azine and aldehyde with alkyne and cycloisomerization toward synthesis of N-fused imidazoles. Unlike previous processes, the present method avoids the requirement of an anaerobic procedure and encompasses versatile heterocyclic amidines toward preparation of diverse motifs in good to high yields. This approach is an inexpensive, simple, general, and environmentally benign way to synthesize N-fused imidazoles, which are of therapeutic interests. This work reveals an inexpensive, eco-friendly, and novel use of $CuSO_4$−glucose as surrogate to efficient Cu(I)−Cu(II) bicatalyst system in organic synthesis.

EXPERIMENTAL SECTION

General Considerations. The starting materials and solvents were used as received from commercial sources without further purification. The ^1H and ^{13}C spectra were recorded in $CDCl_3/CD_3OD$ solvents on a 400 MHz spectrometer using TMS as internal standard. Melting points determined are uncorrected.

Representative Experimental Procedure for the Synthesis of 3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine (Table 2, Entry 1). A mixture of 2-aminopyridine (94 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol) was stirred for 15 min. Ethanol (2 mL) was added, followed by phenylacetylene (153 mg, 1.5 mmol). Then, $CuSO_4 \cdot 5H_2O$ (12.5 mg, 15 mol %) and D-glucose (54 mg, 30 mol %) were added, and the resulting mixture was refluxed at 100 °C (silicon oil bath temperature). After completion of reaction as indicated by TLC (10 h), the resultant mixture was directly adsorbed on neutral alumina (without work up) and purified by column chromatography on neutral alumina (60−325 mesh) eluting with ethyl acetate−hexane. It afforded 3-benzyl-2-phenylimidazo[1,2-*a*]pyridine (224 mg, 79% yield).

All reactions for the synthesis of N-fused imidazoles (Table 2) were carried out following this representative procedure. For solid aldehydes, ethanol (0.2 mL) was used for initial stirring with heterocyclic azines.

3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine (Table 2, Entry 1).[6,8] White crystalline solid: mp 118−120 °C; 224 mg, 79% yield;

IR (KBr) ν_{max} 3073, 2924, 1652, 1602, 1491, 1447, 1352, 1254, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80 −7.77 (m, 2H), 7.70−7.68 (m, 2H), 7.43 (t, J = 6.6 Hz, 2H), 7.37 −7.34 (m, 1H), 7.33 −7.27 (m, 3H), 7.20 −7.16 (m, 1H), 7.15 (d, J = 6.9 Hz, 2H), 6.71 (t, J = 6.8 Hz, 1H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.9, 144.2, 136.8, 134.5, 129.0, 128.6, 128.2, 127.74, 127.72, 126.9,

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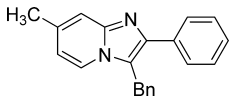
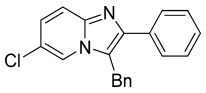
124.2, 123.4, 117.7, 117.6, 112.2, 29.9; MS (APCI) m/z 285 (M + H^+).

3-Benzyl-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (Table 2, Entry 2).[6,8b] Light yellow crystals: mp 144−146 °C; 221 mg, 74%



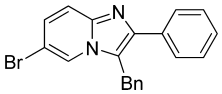
yield; IR (KBr) ν_{max} 2956, 1646, 1494, 1453, 1360, 1259, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.78−7.76 (m, 2H), 7.56 (d, J = 6.9 Hz, 1H), 7.43−7.39 (m, 3H), 7.35−7.31 (m, 3H), 7.28−7.22 (m, 1H), 7.14 (d, J = 6.9 Hz, 2H) 6.52 (dd, J = 6.9 Hz, J = 1.6 Hz, 1H), 4.46 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.3, 143.8, 137.1, 135.1, 134.7, 129.0, 128.6, 128.1, 127.7, 127.6, 126.9, 122.7, 117.0, 115.9, 114.8, 29.9, 21.3; MS (APCI) m/z 299 (M + H^+).

3-Benzyl-6-chloro-2-phenylimidazo[1,2-*a*]pyridine (Table 2, Entry 3). Off-white solid: mp 190−192 °C; 251 mg, 79% yield; IR



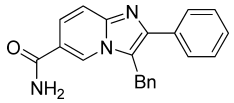
(KBr) ν_{max} 3082, 2925, 1691, 1602, 1492, 1449, 1388, 1249, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, J = 7.6 Hz, 2H), 7.74 (s, 1H), 7.64 (d, J = 9.5 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.38−7.35 (m, 1H), 7.33−7.28 (m, 3H), 7.16−7.13 (m, 3H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.2, 143.2, 136.1, 133.9, 129.2, 128.7, 128.1, 128.0, 127.6, 127.2, 125.6, 121.2, 120.5, 117.9, 29.8; MS (APCI) m/z 319 [M(^{35}Cl) + H^+], 321 [M(^{37}Cl) + H^+] in 3:1 ratio; HRMS (ESI) Calcd for $C_{20}H_{16}ClN_2$ [M + H]$^+$ 319.1002, found m/z 319.0978; Calcd for $C_{20}H_{15}ClN_2Na$ [M + Na]$^+$ 341.0822, found m/z 341.0787.

3-Benzyl-6-bromo-2-phenylimidazo[1,2-*a*]pyridine (Table 2, Entry 4). Off-white crystals: mp > 200 °C; 290 mg, 80% yield; IR



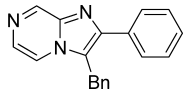
(KBr) ν_{max} 3076, 2924, 1602, 1491, 1448, 1324, 1249, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H); 7.76 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 9.5 Hz, 1H), 7.44−7.40 (m, 2H), 7.37−7.26 (m, 4H), 7.22 (dd, J = 9.5 Hz, J = 1.5 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.0, 143.3, 136.2, 134.0, 129.2, 128.7, 128.1, 128.0, 127.65, 127.58, 127.1, 123.4, 118.24, 118.21, 106.9, 29.8 ; MS (APCI) m/z 363 [M(^{79}Br) + H^+], 365 [M(^{81}Br) + H^+] in 1:1 ratio; HRMS (ESI) Calcd for $C_{20}H_{16}{}^{79}BrN_2$ [M + H]$^+$ 363.0497, found m/z 363.0485.

3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine-6-carboxamide (Table 2, Entry 5). Brown solid: mp > 200 °C; 249 mg, 76% yield; IR



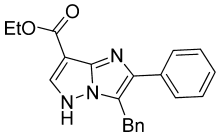
(KBr) ν_{max} 2923, 2361, 1676, 1457, 1377, 1275 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ = 8.44 (s, 1H), 7.78 (d, J = 7.4 Hz, 2H), 7.70 (d, J = 9.1 Hz, 1H), 7.44−7.43 (m, 3H), 7.39−7.36 (m, 1H), 7.33−7.29 (m, 3H),7.13 (d, J = 7.2 Hz, 2H), 5.88 (bs, 2NH), 4.54 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ = 170.8, 149.4, 148.8, 142.4, 139.3, 134.1, 133.9, 133.0, 132.72, 132.69, 131.9, 130.7, 128.6, 124.7, 124.5, 121.2, 33.8; MS (APCI) m/z 328 (M + H) $^+$; HRMS (ESI) Calcd for $C_{21}H_{18}N_3O$ [M + H]$^+$ 328.145, found m/z 328.1435; Calcd for $C_{21}H_{17}N_3ONa$ [M + Na]$^+$ 350.1270, found m/z 350.1253.

3-Benzyl-2-phenylimidazo[1,2-*a*]pyrazine (Table 2, Entry 6). Yellow crystals: mp 110−111 °C; 208 mg, 73% yield; IR (KBr) ν_{max} 2924, 1701, 1629, 1534, 1428, 1260, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.14 (s, 1H); 7.81−7.79 (m, 3H), 7.66 (d, J = 4.2 Hz, 1H), 7.52−7.39 (m, 3H), 7.35 −7.28 (m, 3H), 7.11 (d, J = 6.8 Hz,



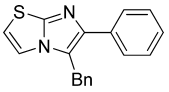
2H), 4.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.5, 140.2, 135.7, 133.5, 129.4, 129.3, 128.9, 128.5, 128.4, 127.6, 127.3, 119.7, 116.5, 29.7; MS (APCI) m/z 286 (M + H^+); HRMS (ESI) Calcd for $C_{19}H_{16}N_3$ [M + H]$^+$ 286.1344, found m/z 286.1323.

Ethyl 3-Benzyl-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carboxylate (Table 2, Entry 7). Yellow powder: mp 98−100 °C; 155



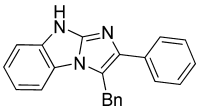
mg, 45% yield; IR (KBr) ν_{max} 2956, 1698, 1610, 1491, 1463, 1224, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.6 (s, 1H), 8.29−8.27 (m, 2H), 8.04−8.02 (m, 2H), 7.62−7.61 (m, 3H), 7.55−7.53 (m, 5H), 7.41−7.39 (m, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.9, 159.1, 148.9, 147.94, 147.86, 136.6, 131.4, 131.2, 130.8, 129.5, 129.0, 128.9, 127.7, 106.4, 103.1, 60.3, 14.6; MS (APCI) m/z 345 (M^+); HRMS (ESI) Calcd for $C_{21}H_{20}N_3O_2$ [M + H]$^+$ 346.1555, found m/z 346.1546 Calcd for $C_{21}H_{19}N_3NaO_2$ [M + Na]$^+$ 368.1375, found m/z 368.1371.

5-Benzyl-6-phenylimidazo[2,1-*b*]thiazole (Table 2, Entry 8). Yellow powder: mp 106−108 °C; 133 mg, 46% yield; IR (KBr) ν_{max}



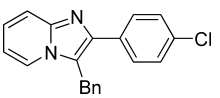
2916, 2219, 1674, 1608, 1260, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.56−7.34 (m, 12H), 5.51 (d, J = 3.24 Hz, 1H), 5.42 (dd, J = 4.1 Hz, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.5, 140.8, 133.3, 131.1, 130.3, 129.5, 129.2, 129.1, 129.0, 126.6, 122.5, 113.0, 55.4; MS (APCI) m/z 291 (MH^+); HRMS (ESI) Calcd for $C_{18}H_{15}N_2S$ [M + H]$^+$ 291.0956, found m/z 291.0940 Calcd for $C_{18}H_{14}N_2SNa$ [M + Na]$^+$ 313.0776, found m/z 313.0776.

3-Benzyl-2-phenyl-9*H*-imidazo[1,2-*a*]benzimidazole (Table 2, Entry 9). Yellow solid: mp > 200 °C; 202 mg, 63% yield; IR



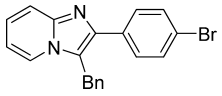
(KBr) ν_{max} 2955, 2372, 1466, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.32 (dd, J = 6.7 Hz, J = 3.2 Hz, 2H), 7.97 (d, J = 8.2 Hz, 1H), 7.74−7.63 (m, 5H), 7.54 (t, J = 3.2 Hz, 3H), 7.46 (t, J = 7.4 Hz, 1H), 7.26 (s, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5, 149.5, 136.7, 132.6, 131.3, 131.1, 129.4, 128.9, 128.4, 127.8, 125.9, 121.2, 120.3, 114.5, 105.3; MS (APCI) m/z 322 (M − H^+); HRMS (ESI) Calcd for $C_{22}H_{16}N_3$ [M − H]$^+$ 322.1344, found m/z 322.1345.

3-Benzyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (Table 2, Entry 10).[8] White solid: mp 146−148 °C; 232 mg, 73% yield; IR



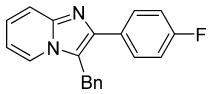
(KBr) ν_{max} 3072, 2851, 1634, 1601, 1488, 1453, 1360, 1247, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.73−7.66 (m, 4H), 7.39 (d, J = 8.6 Hz, 2H), 7.33−7.27 (m, 3H), 7.22−7.18 (m, 1H), 7.12 (d, J = 8.2 Hz, 2H), 6.73 (dt, J = 6.8 Hz, J = 1.1 Hz, 1H), 4.48(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.9, 143.0, 136.5, 133.7, 133.0, 129.4, 129.1, 128.9, 127.6, 127.0, 124.5, 123.4, 117.8, 117.6, 112.4, 29.8; MS (APCI) m/z 319 (M + H^+).

dx.doi.org/10.1021/jo3003024 | J. Org. Chem. 2012, 77, 4438−4444



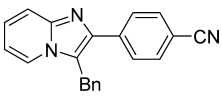
3-Benzyl-2-(4-bromophenyl)imidazo[1,2-*a*]pyridine (Table 2, Entry 11).[6,8b−d] Yellow crystals: decomposes at 160 °C; 257 mg, 71% yield; IR (KBr) ν_{max} 3032, 2928, 1632, 1492, 1445, 1358, 1256, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71−7.69 (m, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 7.32−7.28 (m, 3H), 7.20 (t, J = 8 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 6.73 (t, J = 6.7 Hz, 1H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.9, 143.0, 136.5, 133.5, 131.8, 129.7, 129.1, 127.6, 127.0, 124.5, 123.4, 121.9, 117.9, 117.6, 112.4, 29.8; MS (APCI) m/z 363 [M(^{79}Br) + H^+], m/z 365 [M(^{81}Br) + H^+] in 1:1 ratio.

3-Benzyl-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (Table 2, Entry 12).[6,8a−c] Light yellow oil: 217 mg, 72% yield; IR (neat) ν_{max}



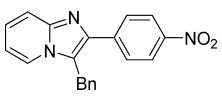
2955, 1603, 1499, 1453, 1359, 1260, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75−7.67 (m, 4H), 7.33−7.27 (m, 3H), 7.20 (dt, J = 6.8 Hz, J = 1.2 Hz, 1H), 7.17−7.09 (m, 4H), 6.72 (dt, J = 7.2 Hz, J = 1.1 Hz, 1H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.6 (d, J_{C-F} = 245 Hz), 144.9, 143.3, 136.6, 130.6, 129.9 (d, $J_{C-C-C-F}$ = 8 Hz), 129.1, 127.7, 127.0, 123.9 (d, J_{C-C-F} = 95 Hz), 117.5, 115.7, 115.5, 112.3, 29.8; MS (APCI) m/z 303 (M + H^+).

4-(3-Benzylimidazo[1,2-*a*]pyridin-2-yl)benzonitrile (Table 2, Entry 13).[6,8b,c] Light yellow solid: mp 134−136 °C; 253 mg, 82%



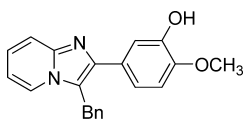
yield; IR (KBr) ν_{max} 3043, 2223, 1676, 1610, 1494, 1450, 1356, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 6.7 Hz, 2H), 7.74 (d, J = 6.8 Hz, 1H), 7.71−7.68 (m, 3H), 7.35−7.28 (m, 3H), 7.24−7.21 (m, 1H), 7.12 (d, J = 6.8 Hz, 2H), 6.77 (dt, J = 6.8 Hz, J = 1.0 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.2, 142.0, 139.1, 136.0, 132.5, 129.2, 128.5, 127.6, 127.2, 125.1, 123.5, 119.0, 117.8, 112.8, 111.1, 29.8; MS (APCI) m/z 310 (M + H^+).

3-Benzyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (Table 2, Entry 14).[8b−d] Yellow solid: mp 156−158 °C; 240 mg, 73% yield; IR



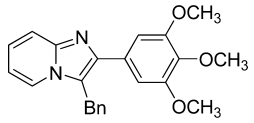
(KBr) ν_{max} 3071, 2925, 2434, 1632, 1598, 1506, 1454, 1336, 1252, 1111 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ = 8.29 (d, J = 7.1 Hz, 2H), 7.96 (d, J = 7.3 Hz, 2H), 7.75−7.69 (m, 2H), 7.32−7.31 (m, 4H), 7.13 (s, 2H), 6.79−6.77 (m, 1H), 4.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.2, 141.3, 137.4, 136.5, 128.9, 128.7, 128.0, 127.7, 127.0, 126.7, 124.9, 123.3, 119.9, 118.0, 112.0, 29.1; MS (APCI) m/z 330 (M + H^+).

5-(3-Benzylimidazo[1,2-*a*]pyridin-2-yl)-2-methoxyphenol (Table 2, Entry 15). Dark yellow solid: mp 102−103 °C; 264 mg,



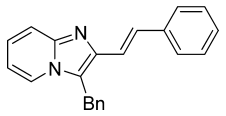
80% yield; IR (KBr) ν_{max} 2925, 1629, 1601, 1501, 1438, 1249, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 6.8 Hz, 1H), 7.41 (s, 1H), 7.30−7.28 (m, 3H), 7.24−7.18 (m, 2H), 7.13 (d, J = 7.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.72 (t, J = 6.7 Hz, 1H), 4.49 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.7, 145.9, 136.6, 129.0, 127.7, 126.9, 124.5, 123.4, 120.2, 117.2, 114.6, 112.4, 110.9, 55.9, 29.8; MS (APCI) m/z 331 (M + H^+); HRMS (ESI) Calcd for $C_{21}H_{19}N_2O_2$ [M + H]$^+$ 331.1446, found m/z 331.1428 Calcd for $C_{21}H_{18}N_2NaO_2$ [M + Na]$^+$ 353.1266, found m/z 353.1244.

3-Benzyl-2-(3,4,5-trimethoxyphenyl)imidazo[1,2-*a*]pyridine (Table 2, Entry 16). Brown solid: mp 86−88 °C; 288 mg, 77% yield;



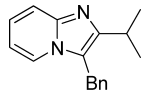
IR (KBr) ν_{max} 2925, 1605, 1502, 1462, 1363, 1242, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 6.4 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.32−7.29 (m, 2H), 7.24−7.19 (m, 2H), 7.13 (d, J = 7.2 Hz, 2H), 6.97 (s, 2H), 6.77 (t, J = 6.8 Hz, 1H), 4.51 (s, 2H), 3.87 (s, 3H), 3.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4, 144.7, 144.0, 137.8, 136.9, 129.9, 129.1, 127.6, 126.9, 124.4, 123.2, 117.6, 117.5, 112.5, 105.2, 60.9, 56.0, 29.9; MS (APCI) m/z 375 (M + H^+); HRMS (ESI) Calcd for $C_{23}H_{23}N_2O_3$ [M + H]$^+$ 375.1708, found m/z 375.1695; Calcd for $C_{23}H_{22}N_2NaO_3$ [M + Na]$^+$ 397.1528, found m/z 397.1509.

(*E*)-3-Benzyl-2-styrylimidazo[1,2-*a*]pyridine ((Table 2, Entry 17). Light orange solid: mp 185−186 °C; 217 mg, 70% yield; IR



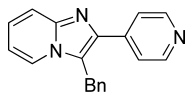
(KBr) ν_{max} 3076, 2923, 1624, 1601, 1491, 1449, 1354, 1252, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.61 (d, J = 9.2 Hz, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.30−7.23 (m, 5H), 7.17−7.13 (m, 3H), 6.66 (t, J = 6.7 Hz, 1H) 4.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.2, 137.4, 136.5, 130.9, 128.9, 128.7, 128.0, 127.7, 127.0, 126.7, 126.5, 124.9, 123.3, 119.9, 118.0, 117.0, 112.1, 29.1; MS (APCI) m/z 311(M + H^+); HRMS (ESI) Calcd for $C_{22}H_{19}N_2$ [M + H]$^+$ 311.1548, found m/z 311.1521.

3-Benzyl-2-isopropylimidazo[1,2-*a*]pyridine (Table 2, Entry 18).[6,8a,b] Yellow crystals: mp 84−86 °C; 50 mg, 20% yield; IR (KBr)



ν_{max} 2925, 1219, 1069, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63−7.59 (m, 2H), 7.28−7.24 (m, 2H), 7.21 (d, J = 7.0 Hz, 1H), 7.09−7.05 (m, 3H), 6.61 (dt, J = 6.6 Hz, J = 1.2 Hz, 1H), 4.28 (s, 2H), 3.26−3.19 (m, 1H), 1.41 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.6, 144.6, 137.2, 128.8, 127.8, 126.7, 123.2, 123.1, 117.1, 116.2, 111.5, 28.9, 26.7, 23.1; MS (APCI) m/z 251 (M + H^+).

3-Benzyl-2-(pyridin-4-yl)imidazo[1,2-*a*]pyridine (Table 2, Entry 19). Off white solid: mp 124−125 °C; 199 mg, 70% yield; IR



(KBr) ν_{max} 3029, 2925, 1605, 1494, 1362, 1275 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ = 8.61 (d, J = 4.6 Hz, 2H), 8.07 (d, J = 6.6 Hz, 1H), 7.80 (d, J = 4.7 Hz, 2H), 7.67 (d, J = 9 Hz, 1H), 7.42−7.38 (m, 1H), 7.32−7.29 (m, 2H), 7.26−7.24 (m, 1H), 7.12 (d, J = 7.1 Hz, 2H), 6.93 (t, J = 6.5 Hz, 1H), 4.63 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ = 150.5, 146.6, 144.1, 140.8, 137.7, 130.2, 128.7, 128.2, 127.6, 125.6, 124.0, 122.4, 117.8, 114.5, 30.1; MS (APCI) m/z 286 (M + H^+); HRMS (ESI) Calcd for $C_{19}H_{16}N_3$ [M + H]$^+$ 286.1344, found m/z 286.1338 Calcd for $C_{19}H_{15}N_3Na$ [M + Na]$^+$ 308.1164, found m/z 308.1141.

3-Benzyl-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine (Table 2, Entry 20).[8d] Greenish-yellow solid: mp 160−162 °C; 191 mg, 66%

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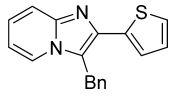
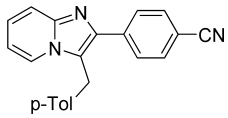


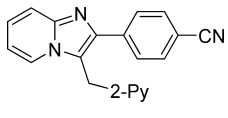
yield; IR (KBr) ν_{max} 2956, 1956, 1460, 1378, 1275, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, J = 6.8 Hz, 1H), 7.66 (d, J = 9.1 Hz, 1H), 7.41 (d, J = 3.1 Hz, 1H), 7.35 (dd, J = 5.1 Hz, J = 0.8 Hz, 1H), 7.30−7.23 (m, 3H), 7.19−7.15 (m, 3H), 7.09 (dd, J = 5.0 Hz, J = 3.6 Hz, 1H), 6.71 (t, J = 6.8 Hz, 1H), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.7, 138.4, 137.4, 136.3, 129.0, 127.79, 127.77, 127.0, 125.6, 124.7, 124.6, 123.2, 117.4, 117.3, 112.5, 29.9; MS (APCI) m/z 291 (M + H^+); HRMS (ESI) Calcd for $C_{18}H_{15}N_2S$ [M + H]$^+$ 291.0956, found m/z 291.0935 Calcd for $C_{18}H_{14}N_2NaS$ [M + Na]$^+$, 313.0776, found m/z 313.0754.

4-(3-(4-Methylbenzyl)imidazo[1,2-*a*]pyridin-2-yl)-benzonitrile (Table 2, Entry 21).[6] Off-white solid: mp 140−141 °C;



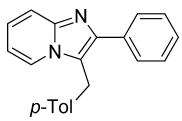
233 mg, 72% yield; IR (KBr) ν_{max} 3092, 2923, 2226, 1695, 1608, 1499, 1443, 1361, 1255, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 6.4 Hz, 1H), 7.71−7.69 (m, 3H), 7.23−7.21 (m, 1H), 7.13 (d, J = 7.1 Hz, 2H), 7.0 (d, J = 7.0 Hz, 2H), 6.76 (t, J = 6.2 Hz, 1H), 4.46 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.1, 141.9, 139.2, 136.9, 132.9, 132.4, 129.9, 128.5, 127.4, 124.9, 123.6, 119.3, 119.0, 117.8, 112.7, 110.9, 29.4, 21.0; MS (APCI) m/z 324 (M + H^+).

4-(3-(Pyridin-2-ylmethyl)imidazo[1,2-*a*]pyridin-2-yl)-benzonitrile (Table 2, Entry 22). Brown solid: mp 166−168 °C;



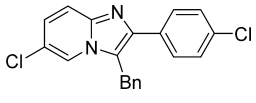
214 mg, 69% yield; IR (KBr) ν_{max} 2956, 2225, 1607, 1459, 1377, 1260, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.6 (dt, J = 4.0 Hz, J = 0.8 Hz, 1H), 7.99−7.95 (m, 3H), 7.73 (d, J = 6.7 Hz, 2H), 7.67 (d, J = 9.1 Hz, 1H), 7.60 (dt, J = 7.7 Hz,, J = 1.8 Hz, 1H), 7.24−7.19 (m, 2H), 7.98 (d, J = 7.9 Hz, 1H), 6.80 (dt, J = 6.8 Hz, J = 1.1 Hz, 1H), 4.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9, 150.0, 145.2, 141.9, 139.2, 137.3, 132.5, 128.7, 125.1, 123.8, 122.3, 121.9, 119.0, 118.5, 117.8, 112.8, 111.1, 33.0; MS (APCI) m/z 311 (M + H^+); HRMS (ESI) Calcd for $C_{20}H_{15}N_4$ [M + H]$^+$ 311.1296, found m/z 311.1279.

3-(4-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (Table 2, Entry 23).[6,8] White crystals: mp 124−126 °C; 212 mg, 71%



yield; IR (KBr) ν_{max} 2924, 1696, 1604, 1446, 1247, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 7.5 Hz, 2H), 7.74 (d, J = 9.4 Hz, 1H), 7.70 (d, J = 6.9 Hz, 1H), 7.45−7.41 (m, 2H), 7.37−7.35 (m, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 6.72 (t, J = 6.7 Hz, 1H), 4.46 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.8, 143.9, 136.6, 133.5, 132.7, 129.9, 129.7, 128.6, 128.3, 127.8, 127.6, 124.3, 123.5, 117.9, 117.5, 112.3, 29.4, 21.0; MS (APCI) m/z 299 (M + H^+).

3-Benzyl-6-chloro-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (Table 2, Entry 24). White crystals: mp 158−160 °C; 275 mg, 78%



yield; IR (KBr) ν_{max} 3076, 2925, 1601, 1493, 1454, 1375, 1241, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, J = 1.1 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 9.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.35−7.27 (m, 3H), 7.16 (dd, J = 9.5 Hz, J = 1.8 Hz, 1H), 7.11 (d, J = 7.0 Hz, 2H), 4.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.0, 143.3, 135.9, 134.0, 132.5, 129.31, 129.27, 128.9, 127.6, 127.3, 125.8, 121.2, 120.7, 118.5, 117.9, 29.8; MS (APCI) m/z 353 (MH^+); HRMS (ESI) Calcd for $C_{20}H_{15}Cl_2N_2$ [M + H]$^+$ 353.0612, found m/z 353.0588; Calcd for $C_{20}H_{14}Cl_2N_2Na$ [M + Na]$^+$, 375.0432, found m/z 375.0419.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra of ^1H for known compounds; spectra of ^1H and ^{13}C for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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