Synthesis of Imidazo[1,2-*a*]pyridines Using Fe_3O_4@SiO_2 as an Efficient Nanomagnetic Catalyst *via* a One-Pot Multicomponent Reaction

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A one-pot multicomponent synthesis of imidazo[1,2-*a*]pyridine derivatives by using pyridin-2-amines, aldehydes, and terminal alkynes in the presence of a catalytic amount of silica-supported iron oxide (Fe_3O_4@SiO_2) nanoparticles in refluxing EtOH in good-to-excellent yields is reported.

Introduction. – Imidazo[1,2-*a*]pyridines have been the object of intense investigations in medicinal chemistry, because of their remarkable central nervous system activity, and are now one of the most widely prescribed classes of psychotropics. They constitute a class of biologically active compounds such as potent anti-inflammatory [1–3] and antibacterial agents [4], inhibitors of gastric acid secretion [5], selective cyclin-dependent kinase inhibitors [6], calcium channel blockers [7][8], β-amyloid formation inhibitors [9], and bradykinin B2 receptor antagonists [10]. Furthermore, they represent the main framework of several established drugs [11–17] such as sedative-hypnotic drugs zolpidem and alpidem [11][12]: zolpidem (**A**), for the treatment of insomnia; alpidem (**B**), an anxiolytic agent; olprinone (**C**) [13][14] for the treatment of acute heart failure; minodronic acid (**D**) [13][14] for the treatment of osteoporosis; zolimidine (**E**) [15], an anti-ulcer agent; necopidem (**F**) [16] and saripidem (**G**) [17] as anxiolytic drugs; and further biologically and pharmaceutically active agents (*Fig. 1*) [13][14].

In recent years, several methods for the synthesis of imidazo[1,2-*a*]pyridine scaffolds have been developed, but most of them are limited in scope or require multistep preparation of the starting materials [18–20]. Among them, due to significant advantages of multicomponent reactions (MCRs) over conventional linear syntheses, such as shorter time, saving energy, and inexpensive raw materials, thus resulting in both economic and environmental benefits [21–23], the reaction of pyridine-2-amines, aldehydes, and terminal alkynes is the most attractive method for the synthesis of imidazo[1,2-*a*]pyridines, which has been carried out using metal-based catalysts such as CuCl/$Cu(OTf)_2$ [24], $CuSO_4$/$TsOH \cdot H_2O$ [25], $InBr_3$ [26], CuI–$NaHSO_4 \cdot SiO_2$ [27], and $CuSO_4$–glucose [28].

In this work, a new protocol for the one-pot three-component synthesis of imidazo[1,2-*a*]pyridine derivatives **4a**–**4j** has been introduced starting from simple and readily available compounds including a pyridin-2-amine **1**, an aldehyde **2**, and a terminal alkyne **3** in the presence of a catalytic amount of silica-supported iron oxide, Fe_3O_4@SiO_2, nanoparticles and K_2CO_3 in refluxing EtOH in good-to-excellent yields

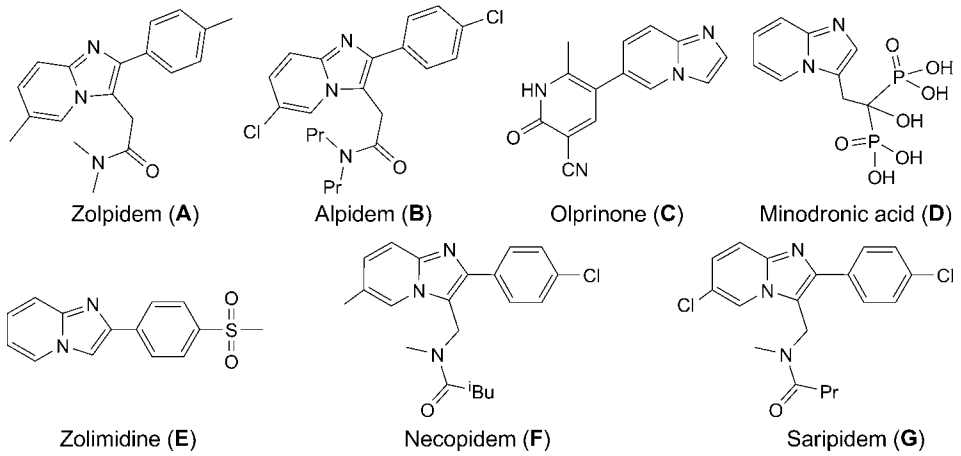
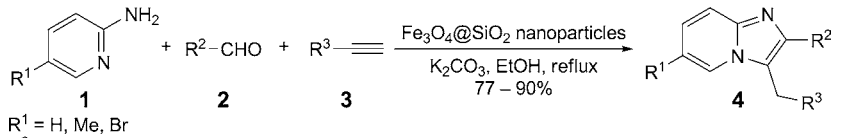


Fig. 1. *Structures of some important drugs containing the imidazopyridine cores*

(*Scheme 1*). This new approach has a potential to access an important field by using economically and environmentally efficient Fe_3O_4@SiO_2 nanoparticles in the synthesis of heterocyclic compounds.

Scheme 1. *Synthesis of Imidazo[1,2-*a*]pyridines* **4a**–**j** *in the Presence of* Fe_3O_4@SiO_2 *Nanocatalyst*



R^1 = H, Me, Br
R^2 = Ph, 4-Me–C_6H_4, 4-Cl–C_6H_4, 4-CN–C_6H_4, 4-NO_2–C_6H_4, naphthalen-2-yl, thien-2-yl, pentyl
R^3 = Ph, 4-Me–C_6H_4

Results and Discussion. – Silica-supported iron oxide (Fe_3O_4@SiO_2) nanoparticles were readily prepared according as described in [29], by the addition of Fe_3O_4 nanoparticles, dispersed in H_2O, to a basic solution of tetraethylorthosilicate (TEOS) and stirring overnight. After heating the resulted gel, the magnetic material was isolated by centrifugation and vacuum-dried to obtain Fe_3O_4@SiO_2 nanoparticles, which were stable under reaction conditions.

The particle size was studied by transmission electron microscopy (TEM), and the identification of Fe_3O_4@SiO_2 nanoparticles was based on the analysis of TEM images. The obtained TEM images of nanoparticles showed clearly a monodispersed spherical shape in which Fe_3O_4 nanoparticles were supported on silica (*Fig. 2*).

To optimize the conditions, a model reaction was carried out with pyridin-2-amine, PhCHO, and phenylacetylene stirred in refluxing EtOH in the presence of Fe_3O_4@SiO_2 nanocatalyst and K_2CO_3 as a base. The progress of the reaction was monitored by TLC. After completion of the reaction, a physical magnetic filtration of the catalyst, followed by an aqueous workup afforded compound **4a** in 86% yield.

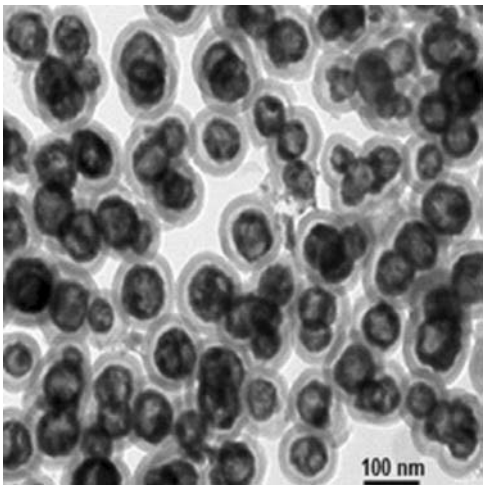


Fig. 2. *TEM Image of the Fe_3O_4@SiO_2 nanoparticles*

The results showed that the efficiency and the yield of the model reaction in EtOH was higher than those obtained in other solvents, such as H_2O, MeOH, MeCN, CH_2Cl_2, and toluene, or under solvent-free conditions.

The above mentioned reaction was also carried out in the presence of various protic solid acids (*Amberlyst-21* and *Montmorillonite-K_{10}*), liquid acids (HCl, H_2SO_4, and AcOH), *Lewis* acid ($AlCl_3$), Fe_3O_4, SiO_2, and K_2CO_3 under the same reaction conditions. The best yield was obtained with Fe_3O_4@SiO_2 nanoparticles. To illustrate the need of the catalyst for this reaction, an experiment was conducted in the absence of Fe_3O_4@SiO_2. The yield in this case was marginal after 8 h. Obviously, Fe_3O_4@SiO_2 is essential for the reaction.

To explore the scope and limitations, various substituted pyridin-2-amines, aldehydes, and terminal alkynes were examined in this MCR. The reaction proceeded very cleanly under mild conditions, and no undesirable side reactions were observed. As compiled in the *Table*, the reaction proceeded efficiently in all of the investigated cases.

An important aspect of this MCR was the high purity of the product. All of the products were sufficiently pure after workup, but they were crystallized from hot EtOH to give highly pure crystalline products.

It was shown that the Fe_3O_4@SiO_2 catalyst could be recovered and reused in subsequent reactions several times without considerable loss of catalytic activity. Thus, this MCR process could be interesting for large-scale syntheses. The catalyst is very active, non-toxic, economically efficient, and environmentally benign. One of the advantages of the heterogeneous catalysts is their reusability. The Fe_3O_4@SiO_2 nanoparticles were adsorbed onto the magnetic stirring bar, when the magnetic stirring was stopped. The nanoparticles were then washed with EtOH, air-dried, and used directly for the next round of reactions without further purification (*Table*, *Entry 1*).

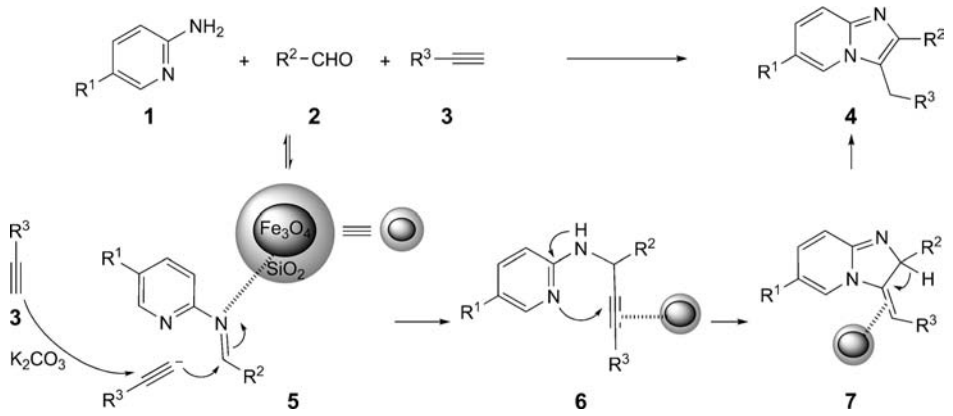
A plausible mechanism for the formation of products **4a** – **4j** is outlined in *Scheme 2*. It is conceivable that the initial event is the formation of imine **5** by condensation of

Table. *Synthesis of Imidazo[1,2-*a*]pyridines* **4a**–**4j** *in the Presence of* Fe_3O_4*@*SiO_2 *Nanoparticles*

Entry	R^1	R^2	R^3	Product	Time [h]	Yield [%][a])
1	H	Ph	Ph	**4a**	3	86[b])
2	Br	4-Me–C_6H_4	Ph	**4b**	4	89
3	H	4-Cl–C_6H_4	Ph	**4c**	4	88
4	H	4-O_2N–C_6H_4	Ph	**4d**	3	83
5	H	Naphthalen-2-yl	Ph	**4e**	5	79
6	H	Pentyl	Ph	**4f**	6	85
7	H	Thiophen-2-yl	4-Me–C_6H_4	**4g**	6	77
8	Me	Thiophen-2-yl	Ph	**4h**	6	84
9	Br	4-CN–C_6H_4	Ph	**4i**	3	90
10	Br	Ph	Ph	**4j**	4	78

[a]) Yields of the isolated products. [b]) Yields of the five subsequent runs by using the same recovered catalyst were 85, 83, 84, 82, and 80%, respectively.

Scheme 2. *Proposed Mechanism for the Formation of the Products* **4a**–**4j**



pyridin-2-amines **1** and aldehydes **2** in the presence of a catalytic amount of Fe_3O_4@SiO_2 and K_2CO_3. Then, intermediate **6** formed from nucleophilic attack of the carbanion form of the terminal alkynes **3** to complex **5**. Cyclization leads to intermediate **7** by intramolecular nucleophilic reaction. Finally, isomerization of compound **7** furnishes the imidazo[1,2-*a*]pyridine derivatives **4a**–**4j**.

In summary, a new protocol for the one-pot multicomponent synthesis of imidazo[1,2-*a*]pyridines starting from simple and readily available precursors including pyridin-2-amines, aldehydes, and terminal alkynes using magnetically recoverable Fe_3O_4@SiO_2 nanocatalyst in the presence of K_2CO_3 as a base has been introduced. This new and efficient MCR approach for the preparation of synthetically, biologically, and pharmaceutically relevant imidazo[1,2-*a*]pyridine derivatives presents some important advantages such as the easy workup procedure, reusability of catalyst, high atom economy, excellent yields, and mild reaction conditions.

The author gratefully acknowledges the financial support from the *Iran National Science Foundation* (INSF) and the *Research Council of the Iran University of Science and Technology* (IUST), and the reviewer for valuable comments and suggestions.

Experimental Part

General. All solvents, chemicals, and reagents were purchased from *Merck*, *Fluka*, and *Sigma-Aldrich*. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-470* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., on *Bruker DRX-500 Avance* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Finnigan-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV; in m/z. Elemental analyses: *Elementar Analysensysteme GmbH VarioEL*. TEM: *Philips EM208*.

Preparation of Silica-Supported Fe_3O_4 Nanoparticles. Dispersion of Fe_3O_4 (< 50-nm particle size (TEM), ≥ 98%) in H_2O (10 ml) was adjusted to pH 11 with NaOH (1M). Then, tetraethyl orthosilicate (TEOS; 2.10 ml) was added, and the mixture was stirred overnight. Then, the resulting gel was heated at 60° during 30 min. The magnetic material was isolated by centrifugation (8,000 rpm, 15 min) and vacuum-dried during 24 h to obtain the Fe_3O_4@SiO_2 nanoparticles.

Representative Synthesis of Compound **4a**. To a reaction tube containing a magnetic stirring bar and Fe_3O_4@SiO_2 nanoparticles (5 mol-%) and K_2CO_3 (5 mol-%) in 5 ml of EtOH, pyridin-2-amine (**1a**; 0.094 g, 1 mmol), PhCHO (**2a**; 0.106 g, 1 mmol) and phenylacetylene (**3a**; 0.102 g, 1 mmol) were added. The mixture was stirred for 3 h under reflux. After completion of the reaction (TLC (AcOEt/hexane 4:1)), stirring was stopped, and the Fe_3O_4@SiO_2 catalyst became attached to the magnetic stir bar. The Fe_3O_4@SiO_2 nanoparticles were then washed with EtOH, air-dried, and used directly for the next round of reactions without further purification. Then, the reaction soln. was filtered off, and the residue was purified by washing with H_2O, and then crystallized from EtOH to give *3-benzyl-2-phenylimidazo[1,2-a]pyridine* (**4a**; 0.245 g, 86%) Light-yellow crystals. M.p. 123–124°. IR (KBr): 3035, 2946, 2850, 1635, 1540, 1440. ^1H-NMR ($CDCl_3$): 4.48 (*s*, CH_2); 6.96 (*t*, *J* = 6.8, 1 arom. H); 7.08 (*d*, *J* = 8.4, 2 arom. H); 7.30–7.90 (*m*, 10 arom. H); 8.16 (*d*, *J* = 9.0, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 29.8; 112.2; 117.4; 123.4; 124.2; 126.9; 127.6; 127.8; 128.2; 128.5; 128.8; 129.0; 129.3; 135.6; 138.8; 144.3. MS: 284 (M^+), 194, 117, 91, 77. Anal. calc. for $C_{20}H_{16}N_2$: C 84.48, H 5.67, N 9.85; found: C 84.51, H 5.55, N 9.79.

3-Benzyl-6-bromo-2-(4-methylphenyl)imidazo[1,2-a]pyridine (**4b**). Yellow crystals. M.p. 207–209°. IR (KBr): 3055, 2926, 2853, 1625, 1530, 1480. ^1H-NMR ($CDCl_3$): 2.36 (*s*, Me); 4.43 (*s*, CH_2); 7.05 (*d*, *J* = 7.1, 2 arom. H); 7.20–7.45 (*m*, 6 arom. H); 7.56 (*d*, *J* = 9.2, 1 arom. H); 7.64 (*d*, *J* = 8.2, 2 arom. H); 7.83 (*s*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 21.5; 29.8; 107.2; 117.4; 123.4; 126.9; 127.1; 127.6; 128.1; 129.1; 129.4; 131.2; 135.6; 137.8; 143.3; 145.2; 148.1. MS: 378 (M^+, ^{81}Br), 376 (M^+, ^{79}Br), 194, 117, 91, 77. Anal. calc. for $C_{21}H_{17}BrN_2$: C 66.85, H 4.54, N 7.43; found: C 66.81, H 4.48, N 7.50.

3-Benzyl-2-(4-chlorophenyl)imidazo[1,2-a]pyridine (**4c**). Yellow crystals. M.p. 170–172°. IR (KBr): 3045, 2944, 2855, 1636, 1545, 1442. ^1H-NMR ($CDCl_3$): 4.45 (*s*, CH_2); 6.50–6.70 (*m*, 2 arom. H); 7.06 (*d*, *J* = 6.1, 1 arom. H); 7.10–7.30 (*m*, 4 arom. H); 7.36 (*d*, *J* = 8.5, 2 arom. H); 7.60–7.70 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 29.8; 112.2; 117.4; 123.4; 124.2; 127.6; 127.8; 128.2; 128.5; 128.8; 129.0; 129.3; 132.6; 133.5; 136.8; 144.5. MS: 320 (M^+, ^{37}Cl), 318 (M^+, ^{35}Cl), 194, 117, 112, 91, 77. Anal. calc. for $C_{20}H_{15}ClN_2$: C 75.35, H 4.74, N 8.79; found: C 75.40, H 4.67, N 8.72.

3-Benzyl-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (**4d**). Yellow crystals. M.p. 157°. IR (KBr): 3055, 2946, 2850, 1630, 1540, 1490, 1350. ^1H-NMR ($CDCl_3$): 4.52 (*s*, CH_2); 6.78 (*t*, *J* = 6.7, 1 arom. H); 7.12 (*d*, *J* = 6.8, 2 arom. H); 7.22 (*s*, 1 arom. H); 7.25–7.40 (*m*, 3 arom. H); 7.72 (*d*, *J* = 8.9, 1 arom. H); 7.78 (*d*, *J* = 6.8, 1 arom. H); 7.98 (*d*, *J* = 8.9, 2 arom. H); 8.26 (*d*, *J* = 8.9, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 29.9; 112.8; 118.1; 119.5; 123.6; 124.2; 125.4; 127.5; 127.8; 128.6; 128.8; 136.2; 139.8; 141.8; 145.3; 147.2. MS: 340 ($[M+1]^+$), 194, 123, 117, 91, 77. Anal. calc. for $C_{20}H_{15}N_3O_2$: C 72.94, H 4.59, N 12.76; found: C 72.89, H 4.54, N 12.60.

3-Benzyl-2-(naphthalen-2-yl)imidazo[1,2-a]pyridine (**4e**). Yellow crystals. M.p. 164–166°. IR (KBr): 3072, 3045, 2946, 2850, 1635, 1540, 1440. ^1H-NMR ($CDCl_3$): 4.28 (*s*, CH_2); 6.70 (*t*, *J* = 6.7, 1 arom. H); 7.06 (*d*, *J* = 7.4, 2 arom. H); 7.10–7.60 (*m*, 8 arom. H); 7.80 (*d*, *J* = 7.7, 2 arom. H); 7.87 (*d*, *J* =

7.8, 2 arom. H); 8.16 (*d*, *J* = 8.0, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 29.7; 112.2; 117.4; 123.5; 124.2; 125.2; 125.8; 126.3; 126.5; 127.0; 127.8; 128.2; 128.5; 128.9; 129.1; 129.2; 130.3; 135.9; 136.3; 138.4; 141.2; 142.5. MS: 334 (M^+), 194, 127, 117, 91, 77. Anal. calc. for $C_{24}H_{18}N_2$: C 86.20, H 5.43, N 8.38; found: C 86.12, H 5.34, N 8.45.

*3-Benzyl-2-pentylimidazo[1,2-*a*]pyridine* (**4f**). Colorless crystals. M.p. 127–128°. IR (KBr): 3038, 2945, 2855, 1635, 1540, 1440, 1346. ^{1}H-NMR ($CDCl_3$): 1.01 (*t*, *J* = 6.8, Me); 1.60–1.90 (*m*, 3 CH_2); 2.83 (*t*, *J* = 6.8, CH_2); 4.28 (*s*, CH_2); 6.64 (*t*, *J* = 7.8, 1 arom. H); 7.10–7.30 (*m*, 6 arom. H); 7.65 (*t*, *J* = 8.9, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 14.3; 23.2; 24.1; 24.2; 29.2; 29.8; 110.3; 111.6; 117.2; 119.2; 123.1; 123.7; 125.8; 126.3; 127.1; 128.8; 137.8. MS: 278 (M^+), 194, 117, 91, 77, 71, 43. Anal. calc. for $C_{19}H_{22}N_2$: C 81.97, H 7.97, N 10.06; found: C 81.85, H 7.81, N 10.15.

*3-(4-Methylbenzyl)-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine* (**4g**). Colorless crystals. M.p. 126–127°. IR (KBr): 3095, 2940, 2852, 1573, 1538, 1492, 1382. ^{1}H-NMR ($CDCl_3$): 2.31 (*s*, Me); 4.48 (*s*, CH_2); 6.68 (*dd*, *J* = 4.4, 4.2, 1 arom. H); 7.05 (*d*, *J* = 4.7, 2 arom. H); 7.10–7.20 (*m*, 4 arom. H); 7.35 (*d*, *J* = 3.1, 1 arom. H); 7.42 (*d*, *J* = 2.8, 1 arom. H); 7.66 (*d*, *J* = 5.4, 1 arom. H); 7.75 (*d*, *J* = 4.1, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 21.2; 29.7; 112.3; 117.4; 117.8; 123.4; 124.5; 124.7; 125.7; 127.6; 127.8; 129.9; 133.3; 136.4; 137.8; 138.6; 144.9. MS: 304 (M^+), 194, 117, 105, 91, 83. Anal. calc. for $C_{19}H_{16}N_2S$: C 74.97, H 5.30, N 9.20; found: C 75.17, H 5.35, N 9.26.

*3-Benzyl-6-methyl-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine* (**4h**). Yellow crystals. M.p. 184–186°. IR (KBr): 3106, 3055, 2916, 2858, 1575, 1539, 1490, 1432, 1385. ^{1}H-NMR ($CDCl_3$): 2.25 (*s*, Me); 4.52 (*s*, CH_2); 7.00–7.10 (*m*, 2 arom. H); 7.16 (*d*, *J* = 7.2, 2 arom. H); 7.30–7.40 (*m*, 7 arom. H). ^{13}C-NMR ($CDCl_3$): 19.2; 29.9; 112.0; 117.4; 118.0; 121.5; 123.0; 125.2; 126.1; 127.6; 128.5; 128.8; 129.8; 130.8; 137.4; 138.3; 144.6. MS: 304 (M^+), 194, 131, 117, 105, 91, 83, 77. Anal. calc. for $C_{19}H_{16}N_2S$: C 74.97, H 5.30, N 9.20; found: C 74.84, H 5.34, N 9.28.

*3-Benzyl-6-bromo-2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine* (**4i**). Light-yellow crystals. M.p. 195–198°. IR (KBr): 3065, 2946, 2850, 2360, 2220, 1615, 1520, 1486, 1412. ^{1}H-NMR ($CDCl_3$): 4.48 (*s*, CH_2); 7.12 (*t*, *J* = 6.8, 1 arom. H); 7.28 (*d*, *J* = 4.7, 2 arom. H); 7.30–7.40 (*m*, 3 arom. H); 7.58 (*d*, *J* = 9.4, 1 arom. H); 7.72 (*d*, *J* = 8.3, 2 arom. H); 7.80–7.90 (*m*, 3 arom. H). ^{13}C-NMR ($CDCl_3$): 29.8; 107.8; 111.3; 118.4; 118.9; 119.4; 123.4; 127.5; 127.6; 128.5; 129.3; 132.6; 135.5; 138.7; 142.8; 143.5; 152.1. MS: 389 (M^+, ^{81}Br), 387 (M^+, ^{79}Br), 194, 117, 102, 91, 77. Anal. calc. for $C_{21}H_{14}BrN_3$: C 64.96, H 3.63, N 10.82; found: C 65.12, H 3.70, N 10.75.

*3-Benzyl-6-bromo-2-phenylimidazo[1,2-*a*]pyridine* (**4j**). Colorless crystals. M.p. 210–212°. IR (KBr): 3085, 2910, 2858, 1575, 1530, 1490, 1450, 1388. ^{1}H-NMR ($CDCl_3$): 4.48 (*s*, CH_2); 7.15 (*d*, *J* = 7.2, 2 arom. H); 7.20–7.50 (*m*, 7 arom. H); 7.56 (*d*, *J* = 9.4, 1 arom. H); 7.76 (*d*, *J* = 7.4, 2 arom. H); 7.85 (*s*, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 29.8; 107.1; 118.1; 118.3; 123.4; 127.3; 127.7; 128.1; 128.3; 128.8; 129.1; 129.3; 134.1; 136.2; 143.3; 145.1. MS: 364 (M^+, ^{81}Br), 362 (M^+, ^{79}Br), 194, 117, 91, 77. Anal. calc. for $C_{20}H_{15}BrN_2$: C 66.13, H 4.16, N 7.71; found: C 66.20, H 4.09, N 7.82.

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Received June 15, 2013