Carbohydrate Building Blocks in the Ugi Three-Component Coupling Reaction: Convenient Annulation of Iminosugars on Imidazoles

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Abstract: An unprecedented version of the Ugi three-component coupling reaction is reported in which isocyanides react with unprotected aldoses as biorenewable aldehyde components and acyclic amidines as amine components. The reaction proceeds through [4 + 1] cycloaddition of a conjugated imine intermediate with the isocyanide followed by dehydrative ring transformation of the resulting 4-amino-5-(polyhydroxyalkyl)imidazole to afford imino sugar-annulated imidazoles in excellent yields (86–95%). The procedure is performed in one pot in the presence of a nanoclay (K-10) catalyst, and can be expeditiously effected under solvent-free microwave-irradiation conditions.

Key words: heterocycles, carbohydrates, cyclizations, multicomponent reactions, catalysis, Ugi reaction

Carbohydrates are important raw materials for the production of organic chemicals, with tailor-made industrial applications, because they are inexpensive, accessible on a ton-scale, and have diverse chemical possibilities.[1] Iminosugars are arousing great interest as potential therapeutic agents against HIV infection,[2] cancer,[3] diabetes,[4] and other genetic and metabolic disorders.[5] Inhibitory activities against carbohydrate-active enzymes have been reported for many naturally occurring iminosugars (e.g., deoxynojirimycin and isofagomine),[6] and migitol,[7] a synthetic glucose-mimetic piperidine, is commercially available in several countries for the treatment of diabetes (Figure 1). Furthermore, several drugs incorporating the imidazo[1,2-*a*]pyridine system are presently in clinical use, e.g. zolimidine (an antiulcer drug), zolpidem (a hypnotic drug), and alpidem (a nonsedative anxiolytic).[8,9]

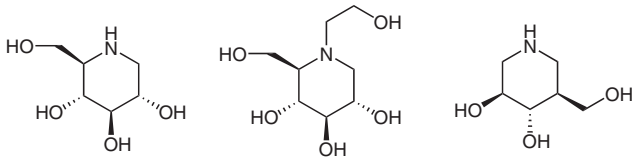
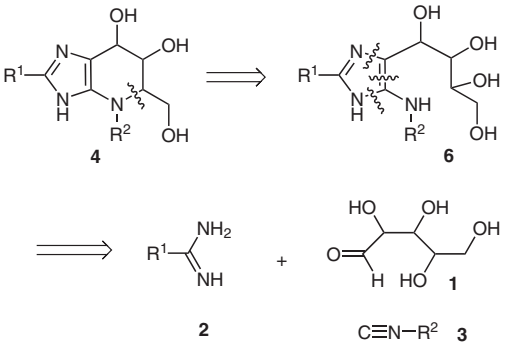


Figure 1 Natural and synthetic iminosugars

The Ugi reaction is one of the most widely used multicomponent reactions, and it offers convenient access to a variety of novel molecular scaffolds. Several methods have been reported in the literature for the synthesis of imidazo[1,2-*a*]pyridines by isocyanide-based Ugi three-component coupling reactions by microwave irradiation in the presence of solid-acid montmorillonite K-10 clay[10] and scandium(III) triflate[11] catalysts. In addition, similar reactions can be performed in ionic liquids,[12] nonpolar solvents,[13] or aqueous media.[14] In all these cases, the synthesis of imidazo[1,2-*a*]pyridines involves the use of 2-aminopyrimidines, aromatic aldehydes, and isocyanides as the building blocks in the Ugi three-component coupling reaction. However, to the best of our knowledge, no variation on the aldehyde building block has been reported, although this could be a significant and useful extension of the reaction for the synthesis of imidazo[1,2-*a*]pyridines. These points prompted us to attempt the annulation of the pharmaceutically important iminosugar moiety onto an imidazole ring by using D-glucose or D-xylose as a new building block in the isocyanide-based Ugi reaction (Scheme 1). This method should not only afford an attractive scaffold for exploiting chemical diversity, but the presence of several free hydroxy groups should render the target molecules water-soluble and biodegradable.



Scheme 1 Disconnection approach to target compound **4**

Most of well-established methods for the synthesis of imidazo[1,2-*a*]pyridines start with the pyrimidine ring and then build up the second imidazole ring by condensation–cyclization reactions involving the nucleophilic cyclic nitrogen. Here we report a conceptually new approach for the synthesis of dihydroxy(polyhydroxyalkyl)imidazopyridines by initial formation of the imidazole ring followed by the construction of the pyridine ring by intramolecular dehydrative cyclization. The synthesis of imidazo[1,2-*a*]pyridines **4** and **5** (Scheme 2) results from the simple disconnection shown in Scheme 1, and from our search for novel solvent-free heterocyclization strategies, especially those using carbohydrates as raw materials.[15] Furthermore, the present work is in accord with the concept of re-

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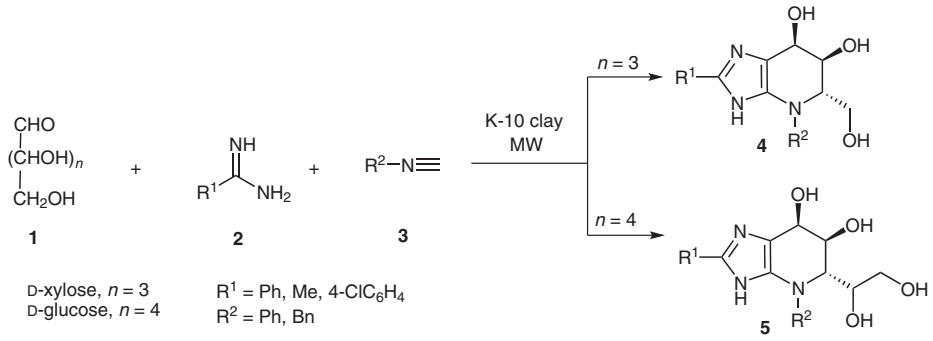
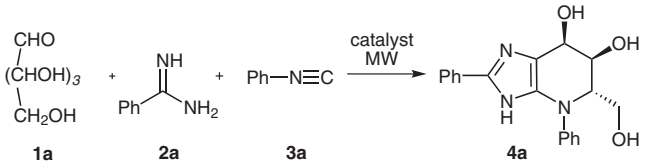


Scheme 2 Synthesis of imidazo[1,2-*a*]pyridines **4** and **5**

newable resources, a new and rapidly developing paradigm in environmental and chemical sciences, involving the widespread use of biorenewable materials for industry.[1]

In our preliminary experiments, we investigated the optimization of the reaction conditions with respect to the catalyst. For this purpose, we chose D-xylose (**1**, n = 3), amidine **2** (R^1 = Ph), and phenyl isocyanide (**3a**, R^2 = Ph) as model substrates for the synthesis of the representative compound **4a** ($R^1 = R^2$ = Ph) (Table 1). We examined various mineral catalysts for the formation of **4a**. Among the catalysts tested, K-10 clay gave the best result (Table 1, entry 1). The $CeCl_3 \cdot 7H_2O$/NaI system and $CeCl_3 \cdot 7H_2O$ afforded the product **4a** in moderate-to-good yields (entries 2 and 3), whereas silica gel and neutral or acidic alumina gave poor yields of **4a** (entries 4–6). No reaction occurred when basic alumina was used as the catalyst. We also observed that significantly lower yields of **4a** were obtained with oil-bath heating than with microwave activation for all the catalyst systems examined (entries 1–6).

Table 1 Optimization of the Catalyst for the Preparation of Compound **4a**



Entry[a]	Catalyst	Microwave heating		Oil-bath heating	
		Time (min)[b]	Yield (%)[c]	Time (h)[b]	Yield (%)[c]
1	K-10 clay	12	91	5	51
2	$CeCl_3 \cdot 7H_2O$	15	53	6	21
3	$CeCl_3 \cdot 7H_2O$, NaI	12	75	8	33
4	silica gel	14	24	8	17
5	neutral alumina	20	13	10	10
6	acidic alumina	20	18	10	13

[a] For details, see the experimental section.
[b] Time for completion of the reaction at 90 °C, as indicated by TLC.
[c] Yield of the isolated and purified product **4a**.

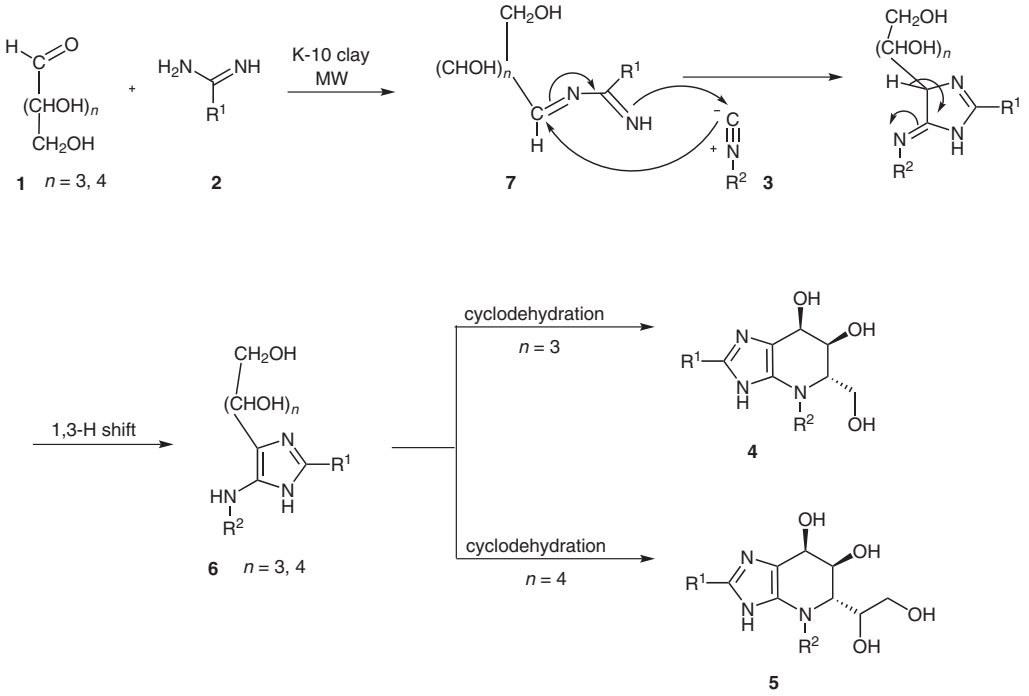
Next, we investigate the substrate scope of the reaction by using a variety of amidines **2** and isocyanides **3** under the optimized reaction conditions. Yields were found to be consistently good (Table 2), the highest being 94% in the case of **4** (entry 5) and 95% in the case of **5** (entry 12).

The optimal conditions for the synthesis involve the use of microwave irradiation of an equimolar, intimate, solvent-free mixture of D-glucose or D-xylose **1**, amidine **2**, and isocyanide **3** with K-10 clay (particle size 32.7 nm), at 90 °C for 12–15 min in a laboratory microwave oven operating on a 230 V, 50 Hz power supply (Table 2). The iminosugar-annulated pyridines **4** and **5** were obtained in 86–95% yield following isolation and purification by crystallization from ethanol.

Table 2 Microwave-Assisted Solvent-Free Synthesis of Products **4**, **5** and **6**

Entry	Product	R^1	R^2	Time (min)[a]	Yield (%)[b,c]
1	**4a**	Ph	Ph	12	91
2	**4b**	Ph	Bn	15	88
3	**4c**	Me	Ph	12	90
4	**4d**	Me	Bn	12	89
5	**4e**	4-ClC_6H_4	Ph	14	94
6	**4f**	4-ClC_6H_4	Bn	12	92
7	**5a**	Ph	Ph	15	91
8	**5b**	Ph	Bn	15	90
9	**5c**	Me	Ph	15	90
10	**5d**	Me	Bn	12	86
11	**5e**	4-ClC_6H_4	Ph	13	92
12	**5f**	4-ClC_6H_4	Bn	12	95
13	**6a**	Ph	Ph	5	67
14	**6c**	Me	Ph	5	58

[a] Time required for completion of the reaction as indicated by TLC.
[b] Yield of isolated and purified products.
[c] All compounds showed satisfactory C, H, and N analyses (± 0.37%) and spectra (IR, ^{1}H NMR, ^{13}C NMR, and EI-MS).



Scheme 3 Plausible mechanism for the formation of imidazo[1,2-*a*]pyridines **4** and **5**

The formation of **4** and **5** may be tentatively rationalized in terms of an initial condensation of aldehyde **1** and amine **2** to give the conjugated bisimine intermediate **7**. This undergoes [4 + 1] cycloaddition with isocyanide **3** followed by a 1,3-H shift to give the imidazole **6** (Scheme 3). Finally, the imidazole **6** undergoes cyclodehydration to give the target compounds **4** or **5** (Scheme 3). The proposed scheme is based on the observation that representative imidazoles **6a** ($n = 3$; $R^1 = R^2 = Ph$) and **6c** ($n = 4$; $R^1 = Me$; $R^2 = Ph$) could be isolated in 58–67% yield and subsequently converted into the corresponding iminosugar-annulated imidazoles **4a** and **5c,** respectively, in quantitative yield.

All the hydroxy and hydroxymethyl groups in the products **4** and **5** are equatorial, as shown by their $J_{H,H}$ values ($J_{H,H}$ = 9.5–9.8 Hz). The chiral carbons of the precursor carbohydrates **1** should retain their configuration in the products **4** and **5** as these atoms are not involved in any bond breaking or bond formation. This view is supported by the observation that there was no change in the absolute configurations of any of the chiral carbon atoms of D-xylose or D-glucose when an intimate solvent-free mixture of either of these sugars (2.0 mmol) with K-10 clay (0.10 g) was subjected to microwave irradiation at 90 °C for 15 min, i.e., under the present reaction conditions. The structures of all the synthesized compounds were established by elemental analysis and by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and EI-MS.

To summarize, we have developed a new version of the Ugi three-component reaction of a biorenewable aldehyde component for the expeditious synthesis of iminosugar-annulated imidazoles of pharmacological potential. This simple and efficient protocol could be a practical alternative to the existing procedures for the synthesis of these types of fine chemicals to cater to the needs of academia and industry.

Melting points were determined by the open glass-capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 + D_2O using TMS as the internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-d_6, and TMS was used as the internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic C, H, and N analyzer. A Chemical Laboratory Microwave Oven (Model; BP-310/50; 230 volt, 50 Hz power input) was used. All chemicals were of reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

Iminosugar-Annulated Imidazoles 4 and 5; General Procedure

An intimate solvent-free mixture of aldose **1** (2.0 mmol), amidine hydrochloride **2**·HCl (2.0 mmol), NaOAc (2.0 mmol), isocyanide **3** (2.0 mmol), and K-10 clay (0.100 g, 10 mol%) in a 20 mL vial was subjected to microwave irradiation at 90 °C for 12–15 min (Table 2). After completion of the reaction (TLC), H_2O (10 mL) was added to the mixture and the crude product was extracted with EtOAc (3 × 10 mL). The extract was filtered, the filtrate was evaporated under reduced pressure, and the residue was crystallized from EtOH to give analytically pure samples of compounds **4** and **5** as a colorless solids.

5-(Hydroxymethyl)-2,4-diphenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (4a)

Colorless solid; mp 135–137 °C.

IR (KBr): 3381, 3319, 3040, 2972, 1630, 1598, 1548, 1455 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.96 (ddd, $J_{2H,3H}$ = 9.8 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, $J_{1'Hb,2H}$ = 2.8 Hz, 1 H, 2-H), 3.46 (dd, $J_{1'Ha,1'Hb}$ = 10.1 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, 1 H, 1′-Ha), 3.61 (dd,

$J_{3H,4H}$ = 9.2 Hz, $J_{2H,3H}$ = 9.8 Hz, 1 H, 3-H), 3.89 (dd, $J_{1'Ha,1'Hb}$ = 10.1 Hz, $J_{1'Hb,2H}$ = 2.8 Hz, 1 H, 1′-Hb), 4.41 (d, $J_{3H,4H}$ = 9.2 Hz, 1 H, 4-H), 6.57–6.71 (m, 3 H, ArH), 7.19–7.51 (m, 7 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 59.2, 60.7, 71.2, 79.3, 115.7, 118.4, 126.8, 127.5, 128.3, 129.0, 129.5, 130.3, 131.1, 132.3, 133.5.

MS (FAB): *m/z* = 338 [M + H$^+$].

Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.35; H, 5.79; N, 12.61.

4-Benzyl-5-(hydroxymethyl)-2-phenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (4b)
Colorless solid; mp 142–145 °C.

IR (KBr): 3383, 3318, 3037, 2975, 1633, 1595, 1551, 1456 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.91 (ddd, $J_{2H,3H}$ = 9.8 Hz, $J_{1'Ha,2H}$ = 5.3 Hz, $J_{1'Hb,2H}$ = 2.9 Hz, 1 H, 2-H), 3.48 (dd, $J_{1'Ha,1'Hb}$ = 10.2 Hz, $J_{1'Ha,2H}$ = 5.3 Hz, 1 H, 1′-Ha), 3.66 (dd, $J_{3H,4H}$ = 9.2 Hz, $J_{2H,3H}$ = 9.8 Hz, 1 H, 3-H), 3.85 (dd, $J_{1'Ha,1'Hb}$ = 10.2 Hz, $J_{1'Hb,2H}$ = 2.9 Hz, 1 H, 1′-Hb), 4.23 (s, 2 H, CH_2), 4.45 (d, $J_{3H,4H}$ = 9.2 Hz, 1 H, 4-H), 7.06–7.45 (m, 10 H, ArH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.7, 59.7, 61.2, 69.8, 80.3, 115.8, 116.2, 127.1, 127.9, 128.8, 129.6, 130.3, 131.2, 131.9, 132.5, 133.3.

MS (FAB): *m/z* = 352 [M + H$^+$].

Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.59; H, 5.86; N, 12.11.

5-(Hydroxymethyl)-2-methyl-4-phenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (4c)
Colorless solid; mp 120–121 °C.

IR (KBr): 3379, 3321, 3041, 2968, 1631, 1602, 1549, 1458 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.31 (s, 3 H, CH_3), 2.99 (ddd, $J_{2H,3H}$ = 9.9 Hz, $J_{1'Ha,2H}$ = 5.3 Hz, $J_{1'Hb,2H}$ = 2.7 Hz, 1 H, 2-H), 3.41 (dd, $J_{1'Ha,1'Hb}$ = 10.1 Hz, $J_{1'Ha,2H}$ = 5.3 Hz, 1 H, 1′-Ha), 3.56 (dd, $J_{3H,4H}$ = 9.2 Hz, $J_{2H,3H}$ = 9.9 Hz, 1 H, 3-H), 3.86 (dd, $J_{1'Ha,1'Hb}$ = 10.1 Hz, $J_{1'Hb,2H}$ = 2.7 Hz, 1 H, 1′-Hb), 4.43 (d, $J_{3H,4H}$ = 9.2 Hz, 1 H, 4-H), 6.71–7.11 (m, 5 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.1, 59.6, 61.2, 70.7, 79.8, 116.7, 118.1, 128.1, 129.1, 130.9, 132.6, 134.1.

MS (FAB): *m/z* = 276 [M + H$^+$].

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.35; H, 6.51; N, 15.04.

4-Benzyl-5-(hydroxymethyl)-2-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (4d)
Colorless solid; mp 127–128 °C.

IR (KBr): 3380, 3320, 3036, 2974, 1628, 1597, 1552, 1459 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.38 (s, 3 H, CH_3), 2.97 (ddd, $J_{2H,3H}$ = 9.9 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, $J_{1'Hb,2H}$ = 2.7 Hz, 1 H, 2-H), 3.46 (dd, $J_{1'Ha,1'Hb}$ = 10.1 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, 1 H, 1′-Ha), 3.58 (dd, $J_{3H,4H}$ = 9.1 Hz, $J_{2H,3H}$ = 9.9 Hz, 1 H, 3-H), 3.91 (dd, $J_{1'Ha,1'Hb}$ = 10.1 Hz, $J_{1'Hb,2H}$ = 2.7 Hz, 1 H, 1′-Hb), 4.26 (s, 2 H, CH_2), 4.41 (d, $J_{3H,4H}$ = 9.1 Hz, 1 H, 4-H), 7.05–7.31 (m, 5 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.8, 52.4, 59.2, 60.7, 71.2, 79.3, 126.1, 127.8, 129.6, 130.3, 131.1, 131.8, 133.9.

MS (FAB): *m/z* = 290 [M + H$^+$].

Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 61.90; H, 6.43; N, 14.74.

2-(4-Chlorophenyl)-5-(hydroxymethyl)-4-phenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (4e)
Colorless solid; mp 121–123 °C.

IR (KBr): 3383, 3316, 3045, 2975, 1631, 1605, 1540, 1451 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 3.02 (ddd, $J_{2H,3H}$ = 9.6 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, $J_{1'Hb,2H}$ = 2.9 Hz, 1 H, 2-H), 3.49 (dd, $J_{1'Ha,1'Hb}$ = 10.5 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, 1 H, 1′-Ha), 3.58 (dd, $J_{3H,4H}$ = 9.2 Hz, $J_{2H,3H}$ = 9.6 Hz, 1 H, 3-H), 3.83 (dd, $J_{1'Ha,1'Hb}$ = 10.5 Hz, $J_{1'Hb,2H}$ = 2.9 Hz, 1 H, 1′-Hb), 4.46 (d, $J_{3H,4H}$ = 9.2 Hz, 1 H, 4-H), 6.61–6.78 (m, 3 H, ArH), 7.21–7.59 (m, 4 H, ArH) 7.78–7.85 (m, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 59.5, 60.8, 70.8, 79.1, 115.3, 119.0, 125.3, 126.1, 126.8, 127.5, 128.8, 129.5, 130.1, 132.5, 133.8.

MS (FAB): *m/z* = 372 [M + H$^+$], 374 [M + H$^+$ + 2].

Anal. Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.62; H, 4.59; N, 11.45.

4-Benzyl-2-(4-chlorophenyl)-5-(hydroxymethyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (4f)
Colorless solid; mp 141–143 °C.

IR (KBr): 3385, 3325, 3044, 2965, 1632, 1593, 1554, 1451 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.91 (ddd, $J_{2H,3H}$ = 9.8 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, $J_{1'Hb,2H}$ = 2.7 Hz, 1 H, 2-H), 3.49 (dd, $J_{1'Ha,1'Hb}$ = 10.0 Hz, $J_{1'Ha,2H}$ = 5.4 Hz, 1 H, 1′-Ha), 3.64 (dd, $J_{3H,4H}$ = 9.2 Hz, $J_{2H,3H}$ = 9.8 Hz, 1 H, 3-H), 3.92 (dd, $J_{1'Ha,1'Hb}$ = 10.0 Hz, $J_{1'Hb,2H}$ = 2.7 Hz, 1 H, 1′-Hb), 4.23 (s, 2 H, CH_2), 4.43 (d, $J_{3H,4H}$ = 9.2 Hz, 1 H, 4-H), 7.04 (d, *J* = 8.6 Hz, 2 H, ArH, 4-ClC_6H_4), 7.08–7.21 (m, 5 H, ArH) 7.41 (d, *J* = 8.6 Hz, 2 H, ArH, 4-ClC_6H_4).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.1, 59.5, 60.3, 71.6, 79.6, 125.3, 126.1, 127.6, 128.5, 129.3, 130.1, 130.8, 131.7, 132.6, 133.5, 134.3.

MS (FAB): *m/z* = 386 [M + H$^+$], 388 [M + H$^+$ + 2].

Anal. Calcd for $C_{20}H_{20}ClN_3O_3$: C, 62.26; H, 5.22; N, 10.89. Found: C, 61.97; H, 5.05; N, 11.26.

5-(1,2-Dihydroxyethyl)-2,4-diphenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (5a)
Colorless solid; mp 148–150 °C.

IR (KBr): 3385, 3315, 3042, 2970, 1635, 1599, 1546, 1457 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.93 (dd, $J_{2H,3H}$ = 9.1 Hz, $J_{1'H,2H}$ = 6.2 Hz, 1 H, 2-H), 3.49 (dd, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{2'Ha,2'Hb}$ = 11.3 Hz, 1 H, 2′-Ha), 3.58 (ddd, $J_{1'H,2H}$ = 6.2 Hz, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{1'H,2'Hb}$ = 2.5 Hz, 1 H, 1′-H), 3.65 (dd, $J_{2H,3H}$ = 9.1 Hz, $J_{3H,4H}$ = 9.5 Hz, 1 H, 3-H), 3.86 (dd, $J_{1'H,2'Hb}$ = 2.5 Hz, $J_{2'Ha,2'Hb}$ = 11.3 Hz, 1 H, 2′-Hb), 4.51 (d, $J_{3H,4H}$ = 9.5 Hz, 1 H, 4-H), 6.59–6.68 (m, 3 H, ArH), 7.08–7.49 (m, 7 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.9, 63.3, 65.9, 67.5, 78.2, 115.1, 118.5, 125.5, 126.2, 126.9, 127.7, 128.5, 129.3, 130.1, 132.9, 134.1.

MS (FAB): *m/z* = 368 [M + H$^+$].

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.75; H, 5.51; N, 11.72.

4-Benzyl-5-(1,2-dihydroxyethyl)-2-phenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (5b)
Colorless solid; mp 158–161 °C.

IR (KBr): 3389, 3319, 3038, 2977, 1641, 1591, 1540, 1463 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.88 (dd, $J_{2H,3H}$ = 9.2 Hz, $J_{1'H,2H}$ = 6.2 Hz, 1 H, 2-H), 3.51 (dd, $J_{1'H,2'Ha}$ = 5.6 Hz, $J_{2'Ha,2'Hb}$ = 11.3 Hz, 1 H, 2′-Ha), 3.54 (ddd, $J_{1'H,2H}$ = 6.2 Hz, $J_{1'H,2'Ha}$ = 5.6 Hz, $J_{1'H,2'Hb}$ = 2.6 Hz, 1 H, 1′-H), 3.63 (dd, $J_{2H,3H}$ = 9.2

Hz, $J_{3H,4H}$ = 9.4 Hz, 1 H, 3-H), 3.89 (dd, $J_{1'H,2'Hb}$ = 2.6 Hz, $J_{2'Ha,2'Hb}$ = 11.3 Hz, 1 H, 2′-Hb), 4.21 (s, 2 H, CH_2), 4.56 (d, $J_{3H,4H}$ = 9.4 Hz, 1 H, 4-H), 7.03–7.46 (m, 10 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.1, 61.7, 63.6, 66.3, 67.1, 78.6, 125.5, 126.2, 126.9, 127.7, 128.5, 129.4, 130.1, 130.8, 132.4, 133.8, 134.7.

MS (FAB): *m/z* = 382 [M + H$^+$].

Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.29; H, 6.32; N, 11.21.

5-(1,2-Dihydroxyethyl)-2-methyl-4-phenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (5c)
Colorless solid; mp 133–135 °C.

IR (KBr): 3378, 3311, 3041, 2978, 1630, 1603, 1545, 1453 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.36 (s, 3 H, Me), 2.98 (dd, $J_{2H,3H}$ = 9.2 Hz, $J_{1'H,2H}$ = 6.5 Hz, 1 H, 2-H), 3.47 (dd, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{2'Ha,2'Hb}$ = 11.5 Hz, 1 H, 2′-Ha), 3.52 (ddd, $J_{1'H,2H}$ = 6.5 Hz, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{1'H,2'Hb}$ = 2.4 Hz, 1 H, 1′-H), 3.64 (dd, $J_{2H,3H}$ = 9.2 Hz, $J_{3H,4H}$ = 9.5 Hz, 1 H, 3-H), 3.85 (dd, $J_{1'H,2'Hb}$ = 2.4 Hz, $J_{2'Ha,2'Hb}$ = 11.5 Hz, 1 H, 2′-Hb), 4.53 (d, $J_{3H,4H}$ = 9.5 Hz, 1 H, 4-H), 7.05–7.51 (m, 5 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.1, 62.2, 63.8, 65.6, 67.8, 78.4, 115.6, 119.2, 126.8, 128.3, 129.8, 130.5, 132.2.

MS (FAB): *m/z* = 306 [M + H$^+$].

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.88; H, 6.64; N, 13.49.

4-Benzyl-5-(1,2-dihydroxyethyl)-2-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (5d)
Colorless solid; mp 144–146 °C.

IR (KBr): 3385, 3315, 3042, 2970, 1635, 1599, 1546, 1457 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.33 (s, 3 H, CH_3), 2.95 (dd, $J_{2H,3H}$ = 9.1 Hz, $J_{1'H,2H}$ = 6.1 Hz, 1 H, 2-H), 3.46 (dd, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{2'Ha,2'Hb}$ = 11.4 Hz, 1 H, 2′-Ha), 3.56 (ddd, $J_{1'H,2H}$ = 6.1 Hz, $J_{1'H,2'Ha}$ = 5.7 Hz, $J_{1'H,2'Hb}$ = 2.4 Hz, 1 H, 1′-H), 3.63 (dd, $J_{2H,3H}$ = 9.1 Hz, $J_{3H,4H}$ = 9.5 Hz, 1 H, 3-H), 3.89 (dd, $J_{1'H,2'Hb}$ = 2.4 Hz, $J_{2'Ha,2'Hb}$ = 11.4 Hz, 1 H, 2′-Hb), 4.25 (s, 2 H, CH_2), 4.56 (d, $J_{3H,4H}$ = 9.5 Hz, 1 H, 4-H), 7.04–7.44 (m, ArH, 5 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.4, 53.6, 62.3, 63.5, 65.6, 67.1, 78.2, 126.2, 127.5, 128.7, 129.8, 130.6, 132.7, 133.8.

MS (FAB): *m/z* = 320 [M + H$^+$].

Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 59.93; H, 6.47; N, 12.91.

2-(4-Chlorophenyl)-5-(1,2-dihydroxyethyl)-4-phenyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (5e)
Colorless solid; mp 157–160 °C.

IR (KBr): 3381, 3318, 3046, 2976, 1631, 1595, 1552, 1452 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.89 (dd, $J_{2H,3H}$ = 9.2 Hz, $J_{1'H,2H}$ = 6.2 Hz, 1 H, 2-H), 3.52 (dd, $J_{1'H,2'Ha}$ = 5.6 Hz, $J_{2'Ha,2'Hb}$ = 11.4 Hz, 1 H, 2′-Ha), 3.60 (ddd, $J_{1'H,2H}$ = 6.2 Hz, $J_{1'H,2'Ha}$ = 5.6 Hz, $J_{1'H,2'Hb}$ = 2.5 Hz, 1 H, 1′-H), 3.63 (dd, $J_{2H,3H}$ = 9.2 Hz, $J_{3H,4H}$ = 9.5 Hz, 1 H, 3-H), 3.84 (dd, $J_{1'H,2'Hb}$ = 2.5 Hz, $J_{2'Ha,2'Hb}$ = 11.4 Hz, 1 H, 2'-Hb), 4.49 (d, $J_{3H,4H}$ = 9.5 Hz, 1 H, 4-H), 6.57–6.74 (m, 3 H, ArH), 7.18–7.57 (m, 4 H, ArH), 7.71–7.92 (m, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.6, 63.8, 66.2, 67.8, 77.8, 117.3, 119.1, 124.8, 125.9, 127.1, 128.7, 129.4, 130.8, 131.6, 133.5, 134.3.

MS (FAB): *m/z* = 402 [M + H$^+$], 404 [M + H$^+$ + 2].

Anal. Calcd for $C_{20}H_{20}ClN_3O_4$: C, 59.78; H, 5.02; N, 10.46. Found: C, 59.51; H, 5.39; N, 10.28.

4-Benzyl-2-(4-chlorophenyl)-5-(1,2-dihydroxyethyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-6,7-diol (5f)
Colorless solid; mp 165–168 °C.

IR (KBr): 3380, 3322, 3034, 2963, 1642, 1604, 1555, 1450 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.89 (dd, $J_{2H,3H}$ = 9.1 Hz, $J_{1'H,2H}$ = 6.2 Hz, 1 H, 2-H), 3.51 (dd, $J_{1'H,2'Ha}$ = 5.6 Hz, $J_{2'Ha,2'Hb}$ = 11.3 Hz, 1 H, 2′-Ha), 3.55 (ddd, $J_{1'H,2H}$ = 6.2 Hz, $J_{1'H,2'Ha}$ = 5.6 Hz, $J_{1'H,2'Hb}$ = 2.6 Hz, 1 H, 1′-H), 3.68 (dd, $J_{2H,3H}$ = 9.1 Hz, $J_{3H,4H}$ = 9.5 Hz, 1 H, 3-H), 3.88 (dd, $J_{1'H,2'Hb}$ = 2.6 Hz, $J_{2'Ha,2'Hb}$ = 11.3 Hz, 1 H, 2′-Hb), 4.19 (s, 2 H, CH_2), 4.53 (d, $J_{3H,4H}$ = 9.5 Hz, 1 H, 4-H), 7.02 (d, *J* = 8.6 Hz, 2 H, ArH), 7.05–7.22 (m, 5 H, ArH), 7.48 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.9, 61.6, 63.5, 66.4, 67.3, 78.1, 125.1, 126.4, 127.2, 127.9, 128.7, 129.5, 130.6, 131.4, 132.3, 133.8, 134.6 (Ph, 4-ClC_6H_4).

MS (FAB): *m/z* = 416 [M + H$^+$], 418 [M + H$^+$ + 2].

Anal. Calcd for $C_{21}H_{22}ClN_3O_4$: C, 60.65; H, 5.33; N, 10.10. Found: C, 60.91; H, 5.52; N, 9.88.

Isolation of Imidazoles 6a and 6c and Their Conversion Into the Corresponding Annulated Products 4a and 5c
The same procedure was followed as that described for the synthesis of **4** and **5**, except that the duration of microwave irradiation was 5 min instead of 12–15 min (Table 2). Adducts **6** were crystallized from EtOH to afford analytically pure samples of **6a** and **6c**. The intermediate compound **6a** or **6c** (2.0 mmol) and K-10 clay (0.100 g, 10 mol%) was then subjected to microwave irradiation for 8–12 min to give the corresponding bicyclic derivatives **4** or **5**, quantitatively. These were isolated and purified as described above.

1-(5-Anilino-2-phenyl-1*H*-imidazol-4-yl)butane-1,2,3,4-tetrol (6a)
Colorless solid; mp 103–105 °C.

IR (KBr): 3385, 3315, 3041, 2979, 1630, 1605, 1585, 1450 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 3.59 (ddd, $J_{2'H,3'H}$ = 3.9 Hz, $J_{3'H,4'Hb}$ = 5.2 Hz, $J_{3'H,4'Ha}$ = 5.5 Hz, 1 H, 3′-H), 3.65 (dd, $J_{3'H,4'Hb}$ = 5.2 Hz, $J_{4'Ha,4'Hb}$ = 10.8 Hz, 1 H, 4′-Hb), 3.81 (dd, $J_{1'H,2'H}$ = 6.8 Hz, $J_{2'H,3'H}$ = 3.9 Hz, 1 H, 2′-H), 3.98 (dd, $J_{3'H,4'Ha}$ = 5.5 Hz, $J_{4'Ha,4'Hb}$ = 10.8 Hz, 1 H, 4′-Ha), 4.19 (d, $J_{1'H,2'H}$ = 6.8 Hz, 1 H, 1′-H), 6.61–6.73 (m, 3 H, ArH), 7.19–7.61 (m, 7 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 63.9, 67.1, 70.8, 73.3, 115.8, 117.5, 119.7, 120.3, 125.5, 126.8, 128.3, 129.2, 130.5, 134.8, 145.2.

MS (FAB): *m/z* = 356 [M + H$^+$].

Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 63.93; H, 6.17; N, 11.45.

1-(5-Anilino-2-methyl-1*H*-imidazol-4-yl)pentane-1,2,3,4,5-pentol (6c)
Colorless solid; mp 117–119 °C.

IR (KBr): 3381, 3313, 3047, 2983, 1630, 1601, 1579, 1455 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ = 2.31 (s, 3 H, Me), 3.45 (dd, $J_{2'H,3'H}$ = 4.1 Hz, $J_{3'H,4'H}$ = 3.8 Hz, 1 H, 3′-H), 3.56 (ddd, $J_{3'H,4'H}$ = 3.8 Hz, $J_{4'H,5'Hb}$ = 5.2 Hz, $J_{4'H,5'Ha}$ = 5.5 Hz, 1 H, 4′-H), 3.66 (dd, 1 H, $J_{4'H,5'Hb}$ = 5.2 Hz, $J_{5'Ha,5'Hb}$ = 10.9 Hz, 5′-Hb), 3.83 (dd, $J_{2'H,3'H}$ = 4.1 Hz, $J_{1'H,2'H}$ = 6.9 Hz, 1 H, 2′-H), 4.01 (dd, $J_{4'H,5'Ha}$ = 5.5 Hz, $J_{5'Ha,5'Hb}$ = 10.9 Hz, 1 H, 4′-Ha), 4.18 (d, $J_{1'H,2'H}$ = 6.9 Hz, 1 H, 1′-H), 6.71–7.58 (m, 5 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.8, 63.5, 67.3, 70.3, 71.2, 73.1, 115.5, 119.7, 121.3, 131.2, 135.2, 138.5, 144.9.

MS (FAB): m/z = 324 [M + H^+].

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.93; H, 6.79; N, 12.66.

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