Metal Catalyzed Synthesis of Pentose-Sugar-Based Chiral 2-Substituted-1H-Benzimidazoles

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Abstract
A metal catalyzed synthetic protocol has been developed using Ti(OBu)₄-CeCl₃ combo catalyst for chemoselective cyclocondensation cumoxidation under mild reaction conditions toward synthesis of a new class of optically pure compounds, 2-(6-benzyloxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxol-5-yl)-6a,10a-dihydro-1H-anthra[1,2-d] imidazole-6,11-dione. All pentose-sugar-based aldehydes react with varies substituted dimethyl, 4-benzoyl and benzoquinoyl o-aromatic diamines (OAD) to afford desired chiral benzimidazoles with excellent isolated yield (77%-88%). In this suitable method chiral 2-Substituted-1H-Benzimidazoles were syntheses in high yields without using any hazardous chemicals or harmful acids. Normal aromatic aldehyde also reacts with varies o-aromatic diamines (OAD) give rise to known 2-Aryl-1H-benzimidazoles. All the target chiral 2-Substituted-1H-Benzimidazoles were characterized by FT-IR, NMR spectral and HR-MS data and also verified M.P of normal aromatic 2-Substituted-1H-benzimidazoles from literature.

Introduction
Syntheses of several benzimidazoles and their analogues have been achieved in the last few decade to examine their biological activities. Developing several methods for the synthesis of benzimidazoles in previous years The chirally modified benzimidazoles are getting tremendous importance due to their potential biological activity and other applications. From the earliest synthesis sugar -based chiral benzimidazoles are found applications in new drug design. To development of sugar-based valuable compounds as drugs and other biological active compounds are very important in recent time. They have also widespread applications in fluorescence chemosensing, crystal engineering, and corrosion science. In the treatments of viral, bacterial and fungal infection used benzimidazoles like heterocycle and their analogues. Benzimidazolines the reduced version of the heterocycles is often called organic hydrides, can act as good reducing agents and good hydrogen storage materials in many organic reactions. In this paper I am developing a chemoselective catalytic system under the milder and acid-free reaction conditions toward synthesis of the new pentose sugar base chiral benzimidazoles because there are some weaknesses in the
current methods. In presences of harmful acids, hazardous chemicals or high temperature sugar molecules can easily decompose. Mostly methods are some limitations mainly in terms of drastic reagents used and reaction conditions, formation of undesired 1,2-disubstituted byproducts (3′, Scheme 1). In this connection, an oxidative cyclization processes are found for affording the sugar based chiral benzimidazoles under the acid-free reaction conditions. To designed and synthesis of the sugar-based chiral benzimidazoles was found in such a way that it must be inexpensive, easily accessible. Two protocols are usually followed. One of them is the coupling of o-aromatic diamines (OAD) with carboxylic acids or their derivatives\textsuperscript{1} and the second route involves condensation of aldehyde with OAD followed by oxidative cyclo-dehydrogenation.\textsuperscript{11} Among the two methods the second approach has become more popular probably because of the ease accessibility of a variety of substituted aldehydes. In recent times investigations involving metal catalyzed cyclization processes are very encouraging. Cyclocondensation cum oxidation is a powerful synthetic tool for synthesis of novel heterocyclic skeletons in one step.\textsuperscript{12-14} Griess and Harrow was first reported synthesis of sugar-based benzimidazoles by through condensation of D-glucose and o-phenylenediamine (OPD) in the presence of hydrochloric acid more than one hundred years ago to afford the open chain sugar derivative as the minor product, and in fact it was the first report for synthesis of benzimidazoles.\textsuperscript{1a,15} However, Maiti and co-workers have established glycal-based chiral benzimidazoles by using \textit{Vo(acac)}\textsubscript{2} - CeCl\textsubscript{3} Combo catalyst.\textsuperscript{16} Cerium is a useful element which have been extensively used in synthetic chemistry. CeCl\textsubscript{3} is a very useful metal catalyst, whose unique behavior is used to synthesis various heterocycle.\textsuperscript{1a,17-21} CeCl\textsubscript{3} the lower oxidation state compound of ceria has shown excellent catalytic activity. Catalytic activity is improved in presence of other metal co-catalysts. Development of such a synthetic protocol is very much essential for construction of pentose-sugar-based chiral benzimidazoles. The main envisioned of my work is 2-substituted-1\textit{H}-benzimidazoles bearing biocompatible chiral sugar moieties in presences of electron donating and withdrawing functional groups are very useful for new drugs design and other applications. Readily available carbohydrates
molecules are one of the relevant classes of natural compounds possess various unique features for which it is widely exploited by the nature and also the synthetic organic chemist. For this I have developed a simple route toward synthesis of new sugar derived chiral benzimidazoles.

**Results And Discussion**

I have been studied a new approach for the synthesis of pentose-sugar-based chiral 2-substituted-1H-benzimidazoles with Ti(OBu)₄-CeCl₃ combo catalyst without using any drastic reagents and harmful acids. There are numerous methods in the literature on the synthesis of 2-substituted-1H-benzimidazoles. I have studied various mild catalyst systems and found the Ti(OBu)₄ and CeCl₃ combo catalyst system for the synthesis of pentose-sugar-based chiral 2-substituted-1H-benzimidazoles. Use of Ti(OBu)₄ as cocatalyst improves the reaction rate and yield. Initial exploration of the reaction is carried out by using chemoselective reagents and metal catalyst toward synthesis of 2-substituted benzimidazoles (3, Scheme 1). For this simultaneous condensation, cyclization and oxidation of aliphatic aldehyde (2) with OPD (1) in presence of versatile combo catalyst Ti(OBu)₄ and CeCl₃ at ambient temperature under oxygen (anhydrous air) afforded 2-substituted benzimidazoles without forming any 1,2-disubstituted byproducts (3’, Scheme 1). In our initial experiments the cyclocondensation cum oxidation behavior of the catalytic is confirmed by synthesis of known 2-aryl-1H-benzimidazoles (3a-j, entry 1-10, Table 1).²²,²³ Various functional groups on the aldehyde (2) with OPD (1) is also examine. This mild catalytic system tolerated both election-rich and election-deficient substituents. Most of the cases the reactions are very clean with excellent yield (75%-90%) and reactions are completed within 10-18 hrs. Thus 4-Bromobenzaldehyde (2a) reacts with o-phenylenediamine (1a) to afford 2-(4-bromophenyl)-1H-benzimidazoles with excellent yield (3a). The successful reagents then applied to examine for the synthesis of pentose-sugar-based chiral 2-Substituted-1H-benzimidazoles. All o-aromaticdiamine (OAD, Compounds 1), Ti(OBu)₄ and CeCl₃ were purchases from Sigma Aldrich Chemicals company. All protected sugar-based precursor (4) were synthesized as per the literature (Scheme 2).

**Synthesis of sugar-based precursor:**
Synthesis of 6-alkyloxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole-5-carbaldehyde (4):

Synthesis of the Glucose-based protected pentose-sugar aldehyde precursors (4a,b) is depicted in Scheme 2. Glucose was converted into diacetonide (A) upon treatment with dry acetone and concentrated sulfuric acid (Scheme 2). This protected form was O-alkylated (B, R= benzyl/ methyl,) after formation of alkoxide using NaH in DMF. It was selectively deprotected to C by treatment of 70% aqueous acetic acid. Finally, oxidation with NaIO₄ resulted the desired aldehydes, 6-alkyloxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole-5-carbaldehyde (4a, 4b).

Synthesis of pentose-sugar-based chiral benzimidazoles:

Chemoselective synthetic procedure is applied toward synthesis of chiral benzimidazole utilizing commonly used pentose sugars (Scheme 3). Glucose-based protected pentose-sugar aldehyde, 6-alkyloxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole-5-carbaldehyde (4a,b) are allowed to react under similar reaction condition with dimethyl, 4-benzoyl and benzoquinoyl (1b-d) to afford desired chiral benzimidazoles with excellent isolated yield (77-88%, entry 1-5, Table 2). In all cases the reaction was very clean. The products are determined by FT-IR, NMR and HR-MS methods after purification by column chromatography. A number of new pentose-sugar-based chiral benzimidazoles are synthesized in this mild catalytic approach. All the compounds are reported in first time.

Experimental

All chemicals and solvents are used AR grade. ¹H -NMR spectra were recorded on Bruker 300 MHz spectrometer in CDCl₃. Infrared spectra were recorded on a Perkin-Elmer spectrometer as KBr disc. Optical rotations of all sugar-based chiral 2-substituted-1H-benzimidazoles were measured on Polarimeter (Perkin-Elmer). Organic solvent was dried with Magnesium sulfate. Mass spectra were obtained using high-resolution electrospray ionization in positive ion mode. The chromatographic stationary phase was silica gel. Solvents were evaporated under reduced pressure.

Ti(OBu)₄-CeCl₃ catalyzed synthesis of 2-substituted-1H-benzimidazoles:

A mixture of aromatic benzaldehyde 2 (1.0 mmol), o-aromatic diamines (OAD) 1 (1.0 mmol), anhydrous CeCl₃ (50 mg, 0.20 mmol), THF (5.0 mL), and anhydrous MgSO₄ (0.2 g) in a round-
bottomed flask was stirred at room temperature. Titanium (IV) butoxide was added drop wise (68 mL, 0.20 mmol), and the content was allowed to attain room temperature. The reaction was monitored by TLC [SiO₂ plate, ethyl acetate-petroleum ether] and developed by placing in an iodine chamber. The reaction was complete after 10-18 h. Solvent of the post reaction mixture was removed in a rotary evaporator under reduced pressure at room temperature. The residue of the post reaction mixture was stirred with saturated aqueous bicarbonate solution (20 mL) for 30 min and extracted with ethyl acetate (2 x 25 mL). The organic portion was washed with water (3 x 25 mL), dried on activated sodium sulphate and concentrated in a rotary evaporator under vacuum at room temperature. The crude product was washed with ether to afford pure 2-substituted benzimidazoles (3) in good to excellent yield. Thus, the reaction of 4-Bromobenzaldehyde (2a, 185 mg, 1.0 mmol) with o-Phenylenediamine (1a, 108mg, 1.0 mmol) afforded 2-(4-Bromophenyl)-1H-benzimidazole (3a) after processing in an isolated yield of 88% (240 mg, 0.88 mmol). Compound 3a and all other 2-Aryl-1H-benzimidazoles (3) were also prepared by similar procedure. All compounds (3a-3j) were characterized by comparing the literature melting points and also by ¹H and ¹³C NMR (NDC & DEPT), FT-IR, Mass spectra (El-MS) and elemental analysis. Compounds 3a¹³, 3b²³c, 3c²³c, 3d¹³, 3e²³b, 3f²⁴, 3g¹⁶, 3h¹⁶, 3i¹⁶ and 3j²³c are known in the literature.

**Characterization Data of 2-(4-Bromophenyl)-1H-benzimidazole (3a):**

Yield: 81% (219 mg, 0.81 mmol).

Characteristic: Light Yellow solid.

Melting point: 298 °C. [Lit.¹³ 299-300 °C].

IR (neat, cm⁻¹): 961, 1011, 1112, 1273, 1318, 1429, 1590, 2782, 2855, 2933, 3052.

¹H NMR (300 MHz, DMSO-d₆): d 7.19 (2H, d, J = 5.4 Hz), 7.49 (1H, d, J = 7.2 Hz), 7.63 (1H, d, J = 6.6 Hz), 7.72 (2H, d, J = 8.4 Hz), 8.08 (2H, d, J = 8.4 Hz), 12.96 (1H, s).

¹³CNMR (75MHz, DMSO-d₆): d 121.8, 123.1, 127.7, 128.7, 131.2, 150.2.

**Synthesis of pentose sugar-based Chiral 2-substituted-1H-benzimidazoles by Ti(OBu)₄-**
CeCl₃:

**Synthesis of compound 6a:**

A mixture of 6-benzyloxy/methoxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole-5-carbaldehyde 4a (278 mg, 1.0 mmol) with 1,2-diamminoanthraquinone (1d, 1.0 mmol), anhydrous cerium(III) chloride (50 mg, 0.20 mmol), THF (5.0 mL), and anhydrous MgSO₄ (200 mg) in a round-bottomed flask was stirred at 0 °C. Titanium(IV) butoxide was added drop wise (68 mL, 0.20 mmol), and the content was heated at 50 °C on a hot water bath. The reaction was complete after 10-14 h. The post reaction mixture was filtered through a sintered funnel and the residue was extracted with dichloromethane (2 x 15 mL). The organic portion was washed with water (3 x 15 mL), dried on activated sodium sulfate and concentrated in a rotary evaporator under reduced pressure at room temperature. The crude product was chromatographed on silica gel (60-120 mesh) and eluted with ethyl acetate-petroleum ether (60 °C-80 °C). Thus, the reaction of 6-benzyloxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole-5-carbaldehyde (4a, 278 mg, 1.0 mmol) with 1,2-diamminoanthraquinone (1d, 238 mg, 1.0 mmol) afforded 2-(6-benzyloxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxol-5-yl)-6a,10a-dihydro-1H-anthra[1,2-d]imidazole-6,11-dione (6a) after processing in an isolated yield of 88% (449 mg, 0.88 mmol). Compound 6a and all other benzimidazoles (6) were also prepared by similar procedure. The new pentose-sugar-based chiral benzimidazoles (6a-e) were characterized by ¹H and ¹³C NMR, FT-IR and mass (HR-MS) spectral analyses and measuring their optical rotation.

**Characterization data of new pentose-sugar-based chiral 2-substituted-1H-benzimidazole:**

2-((3aR,5R,6S,6aR)-6-(benzyloxy)-tetrahydro-2,2-dimethylfuro[3,2-d][1,3]dioxol-5-yl)-1H-anthra[1,2-d]imidazole-6,11(6aH,10aH)-dione (6a):

Yield: 88% (449 mg, 0.88 mmol).

Characteristic: Yellow viscous liquid.

[α]_{D}^{20} -17° (c 1.00, CH₃OH).

FT-IR (neat, cm⁻¹): 620, 726, 854, 1030, 1081, 1165, 1217, 1291, 1374, 1453, 1588, 1664, 1724, 1958, 2249, 2860, 3067, 3446.
$^1$H NMR (300 MHz, CDCl$_3$): d 1.35 (3H, s), 1.49 (3H, s), 4.14 (1H, d, $J = 12.0$ Hz), 4.31-4.68 (2H, m), 4.67 (1H, d, $J = 3.3$ Hz), 5.57 (1H, d, $J = 2.8$ Hz), 6.10 (1H, d, $J = 3.3$ Hz), 6.81 (2H, d, $J = 5.7$ Hz), 6.97-6.99 (3H, m), 7.68-7.72 (2H, m), 7.80 (1H, d, $J = 9.0$ Hz), 8.11-8.24 (3H, m), 11.16 (1H, s).

$^{13}$C NMR (75MHz, CDCl$_3$): d 26.3, 26.9, 72.7, 77.7, 83.0, 83.6, 105.5, 112.7, 118.1, 118.3, 121.4, 125.5, 126.4, 127.3, 127.4, 127.8, 128.7, 128.8, 131.8, 133.2, 133.7, 134.2, 136.5, 148.3, 155.5, 182.8, 184.4.

HR-MS ($m/z$) for C$_{29}$H$_{27}$N$_2$O$_6$ (M+H): Calculated 499.1869, Found 499.1875.

2-((3aR,5R,6S,6aR)-tetrahydro-6-methoxy-2,2-dimethylfuro[3,2-d][1,3]dioxol-5-yl)-1H-anthra[1,2-d]imidazole-6,11(6aH,10aH)-dione (6b):

Yield: 80% (338 mg, 0.80 mmol).

Characteristic: Orange viscous liquid.

$[\alpha]_D^{20}$ +11.7° (c 1.00, CH$_3$OH).

FT-IR (neat, cm$^{-1}$): 713, 1023, 1077, 1298, 1670, 2852, 2924, 3441.

$^1$H NMR (300 MHz, CDCl$_3$): d 1.34 (3H, s), 1.52 (3H, s), 3.14 (3H, s), 4.12 (1H, d, $J = 3.0$ Hz), 4.69 (1H, d, $J = 6.0$ Hz), 5.56 (1H, d, $J = 3.0$ Hz), 6.10 (1H, d, $J = 3.0$ Hz), 7.19 (1H, s), 7.69-7.75 (2H, m), 8.01 (1H, d, $J = 8.4$ Hz), 8.14-8.26 (2H, m), 11.16 (1H, m), 8.24-8.26 (1H, m), 11.27 (1H, s).

$^{13}$C NMR (75MHz, CDCl$_3$): d 26.3, 26.9, 58.3, 82.1, 85.6, 105.4, 112.7, 125.6, 126.5, 127.5, 128.7, 133.2, 133.8, 134.2, 148.3, 155.4, 182.8, 184.6.

HR-MS ($m/z$) for C$_{23}$H$_{23}$N$_2$O$_6$ (M+H): Calculated 423.4385, Found 423.4380.

(2-((3aR,5R,6S,6aR)-6-(benzyloxy)-tetrahydro-2,2-dimethylfuro[3,2-d][1,3]dioxol-5-yl)-1H-benzo[d]imidazol-6-yl)(cyclohexa-2,4-dienyl)methanone (6c):

Yield: 77% (362 mg, 0.77 mmol).

Characteristic: Yellow viscous liquid.

$[\alpha]_D^{20}$ -22.4° (c 1.00, CH$_3$OH).

FT-IR (neat, cm$^{-1}$): 710, 885, 1075, 1220, 1316, 1550, 1625, 1980, 2230, 2920, 3282.
\(^1\)H NMR (300 MHz, CDCl\(_3\)): d 1.29 (3H, s), 1.47 (3H, s), 3.80-3.93 (1H, m), 4.21-4.58 (2H, m), 5.01 (1H, 
\(d, J = 1.8 \text{ Hz}\),) 5.56-5.61 (1H, m), 5.86-5.88 (1H, m), 6.72 (2H, \(d, J = 9.0 \text{ Hz}\), 7.00-7.13 (3H, m), 7.19-7.26 (2H, m), 7.40-7.50 (2H, m), 7.68-7.84 (3H, m ), 8.07 (1H, s).

\(^13\)C NMR (75MHz, CDCl\(_3\)): d 26.1, 26.6, 46.2, 73.0, 83.5, 84.7, 104.8, 105.3, 111.7, 112.2, 115.2, 118.9, 124.4, 127.4, 127.6, 127.8, 128.0, 128.3, 128.6, 130.4, 131.9, 136.3, 137.0, 138.2, 145.1, 150.8, 196.6.

HR-MS (m/z) for C\(_{28}\)H\(_{27}\)N\(_2\)O\(_5\) (M+H): Calculated 471.1920, Found 471.1925.

\((2-((3aR,5R,6S,6aR)-tetrahydro-6-methoxy-2,2-dimethylfuro[3,2-d][1,3]dioxol-5-yi)-1H-
benzo[d]imidazol-6-yl)(phenyl)methanone (6d):

Yield: 84% (331 mg, 0.84 mmol).

Characteristic: Orange viscous liquid.

\([\alpha]_D^{20}\) -34.1° (c 1.00, CH\(_3\)OH).

FT-IR (neat, cm\(^{-1}\)): 718, 1027, 1081, 1221, 1309, 1448, 1652, 1719, 2101, 2932, 3285.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): d 1.35 (3H, s), 1.53 (3H, s), 3.16 (3H, s), 4.17 (1H, \(d, J = 3.0 \text{ Hz}\), 4.70 (1H, 
\(d, J = 3.0 \text{ Hz}\),), 5.60 (1H, \(d, J = 3.0 \text{ Hz}\),), 6.03 (1H, \(d, J = 6.0 \text{ Hz}\),) 7.43 (2H, \(t, J = 9.0 \text{ Hz}\),) 7.51-7.58 (1H, 
\(m, J = 9.0 \text{ Hz}\),) 7.74-7.86 (3H, m), 8.10 (1H, s).

\(^13\)C NMR (75MHz, CDCl\(_3\)): d 26.2, 26.8, 58.01,79.7, 80.2, 105.6, 112.7, 115.3, 118.4, 123.8, 125.9, 126.2, 128.8, 133.7, 134.2, 134.5, 145.7, 155.6, 185.2.

HR-MS (m/z) for C\(_{22}\)H\(_{23}\)N\(_2\)O\(_5\) (M+H): Calculated 395.1607, Found 395.1609.

\(2-((3aR,5R,6S,6aR)-6-(benzyloxy)-tetrahydro-2,2-dimethylfuro[3,2-d][1,3]dioxol-5-yi)-1H-
benzo[d]imidazole-6-yl)(phenyl)methanone (6d):

Yield: 82% (323 mg, 0.82 mmol).

Characteristic: Reddish viscous liquid.

\([\alpha]_D^{20}\) -31.5° (c 1.00, CH\(_3\)OH).

FT-IR (neat, cm\(^{-1}\)): 735, 1030, 1082, 1220, 1452, 1724, 2861, 2927, 3417.
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(d\) 1.30 (3H, s), 1.50 (3H, s), 2.36 (6H, s), 4.10-4.17 (2H, m), 4.33 (1H, d, \(J = 3.0\) Hz), 4.68 (1H, d, \(J = 3.0\) Hz), 5.60 (1H, s), 6.07 (H, d, \(J = 3.3\) Hz), 6.90 (2H, d, \(J = 9.0\) Hz), 7.15-7.26 (3H, m), 7.34 (2H, d, \(J = 3.0\) Hz).

\(^{13}\)C NMR (75MHz, CDCl\(_3\)): \(d\) 14.0, 26.3, 26.8, 31.8, 72.8, 77.7, 83.2, 83.5, 105.1, 112.5, 127.6, 127.7, 127.8, 127.9, 128.3, 128.6, 131.6, 136.8, 148.4.

HR-MS (m/z) for C\(_{23}\)H\(_{27}\)N\(_2\)O\(_4\) (M+H): Calculated 395.1971, Found 395.1975.

Conclusion
In this paper, I have described an efficient synthesis protocol for synthesis of sugar-base aldehyde with \(\sigma\)-aromaticdiamine (OAD) is under mild oxidative reaction conditions to afford valuable 2-substituted benzimidazoles. Ti(OBu)\(_4\)-CeCl\(_3\) is found as an efficient catalyst for this reaction to produce a number of desired ubiquitous heterocycles in excellent yield under neutral reaction conditions.

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Tables
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Figures

Scheme 1. Synthesis of 2-aryl-1H-benzimidazoles (3)

Scheme 2. Synthetic procedure for synthesis of 6-alkyloxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole-5-carbaldehyde (4a and 4b)
Scheme 3. Synthesis of chiral 2-substituted-1H-benzimidazole of pentose-sugar

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