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Bi (III) CATALYZED ONE POT-TWO COMPONENT APPROACH: SYNTHESIS OF 2-AMINOARYL BENZIMIDAZOLE

S N Murthy Boddapati,[1*] Bhuvaneswari Chalapaka,[1] Satish V A N,[1] Srinivas Pilli[1]

[1]*Dept. of Chemstry, Sir C R Reddy College, Eluru, Andhra Pradesh, India-534007.*
*Corresponding author, E-mail:*snmurthyboddapati@gmail.com

ABSTRACT
Using inexpensive bismuth catalyst, a simple, one-pot, and effective process was described to construct different 2-aminoarylbenzimidazoles. Initially, *o*-phenylenediamines were treated with phenylisothiocyanates to produce the respective thiourea derivatives. The obtained thiourea derivatives on Bi(III) catalyzed desulfurization and intra molecular *C-N* bond formationreactions forms the consecutive 2-aminoatyl benzimidazoles. The reaction practices are trouble-free, general with brilliant substrate tolerance. This method can quickly access a substituted 2-aminoarylbenzimidazole series in good to exceptional yields in a single preparative step and without the need for chromatography by accommodating a variety of substituent's on both substrates.

KEYWORDS: Bismuth Catalyst, Desulfurization, *C-N* Cross-Coupling, One-Pot, 2-arylaminobenzimidazole.

1. INTRODUCTION

Heterocyclic compounds, such as benzimidazoles, are essential molecules instituted in an array of bio-active substances, both natural and artificial sources[i]. Benzimidazole derivatives are a significant class of heterocycles that contain nitrogen and have a variety of therapeutic uses, like anti-malarial, anti-tubercular[ii], proton-pump inhibitors[iii], antihistamine[iv], antianalgesic[v], anti-inflammatory, antioxidant[vi], anti-microbial[vii, viii], antidiabetic[ix], anti-hypertensive[x], anticancer [xi, xii], anti-ulcer [xiii, xiv], etc. In particular, numerous benzimidazole derivatives, have been identified as strong bioactive substances with potential applications in medicine (Figure 1).[xv-xviii] In addition, these motifs have also been identified as inhibitors of poly(ADP-ribose)polymerase (PARP)[xix], microtubule, dihydrofolate reductase andproteinkinase[xx, xxi], and non-peptide thrombin [xxii], inhibitors.

Thus the construction of these moieties seizes the attention of the synthetic chemists of the world. Accordingly, the developed classical methods involve the (i) 1-benzimidazolylidenehydrazine diazotization[xxiii]; (ii) cyclo condensation of diaminobenzene

with esters under microwave conditions[xxiv]; (iii) *via* solid phase route[xxv]; (iv) by inter molecular cyclocondensation of either carboxylic acids or aldehydes with 2-aminophenylaniline precursor go after by oxidation[xxvi]; (v) sodium dithionite mediated reductive cyclization of aldehyde with *o*-nitro aniline[xxvii]. But, many of these protocols have drawbacks such as strong alkaline conditions, difficult chemical procedures, limited substrate scope, tedious purification practice and soaring temperatures etc.

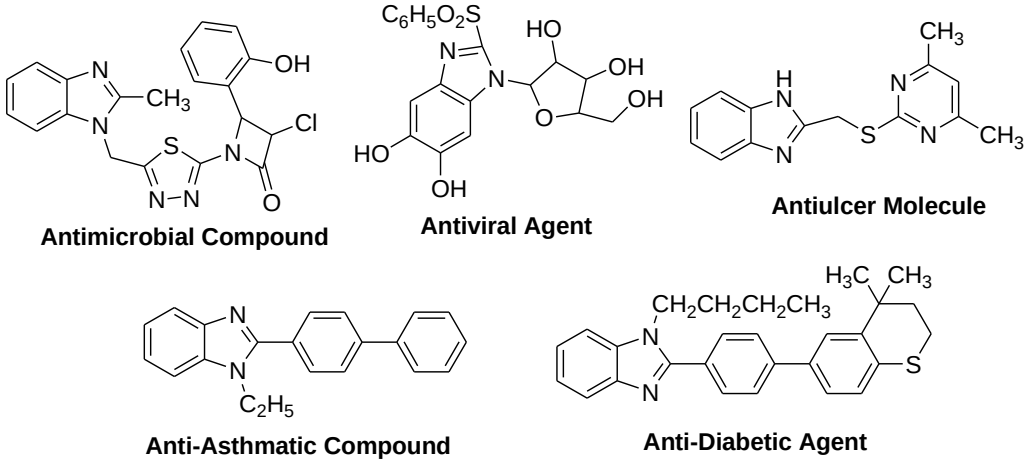


Figure 1. Some important bio-active benzimidazole scaffolds.

Effective protocols for the construction of heterocyclic compounds using metal catalysts have been reported in last ten years,[xxviii] especially for benzimidazole scaffolds. For instance, DaweiMa group described the cascade approach for the development of different benzimidazole derivatives[xxix]. Intramolecular C-X (X=N,S,O) bond construction was customarised by Batey's *et al.*,[xxx] to obtain the amino benzimidazoles. Buchwald group have developed *N*-alkylbenzimidazoles[xxxi]. In addition, *C-N* bond construction by using various transitions metals has been investigated deeply, such as Pd[xxxii], Zn[xxxiii], Cu[xxxiv], Co[xxxv], Ru[xxxvi] for the construction of diverse heterocyclic scaffolds. Recently, Cobalt catalysis has recently been used to produce 2-aminophenyl benzimidazoles from thiourea, but synthesis from bromo precursors has not been successful[xxxvii]. This disadvantage has been overcome by Bollikolla group[xxxviii] by copper catalyzed synthesis of 2-aminoarylbenzimidazoles. However, as far as we are aware, no report has been made available using the current reporting strategy for the synthesis of substituted 2-aminophenylbenzimidazoles using bismuth catalyst. As a result, we would like to outline here the process for the moderately reaction-controlled condensation and Bi-catalyzed desulfurization of benzene phenyldiamine and arylisothiocyanates to produce 2-arylamino benzimidazoles. One more benefit of our approach is that we use Bi catalyst instead of cobalt or copper, which is more affordable, more air stable, and more readily available.

Currently, Bi(III) compounds engrossed great interest in organic transformations owing to their inexpensiveness, thermal stability, high acidity and less toxicity[xxxix], Moreover, $Bi(NO_3)_2$ is described as an environmentally benevolent nitrating agent for selective nitration of organic molecules[xl,xli]. Literature survey disclosed that *N*-benzoylthioureas guanidylation[xlii], Paal–Knorr synthesis of pyrroles[xliii], dihydropyrimidinones[xliv], synthesis of coumarins[xlv], chemo selective synthesis of acylals[xlvi] *etc.*, were effectively described using bismuth nitrate catalyst. As a result, in this work we like to investigate the efficacy of the bismuth nitrate as catalyst

towards the construction of targeted 2-aminoarylbenzimidazoles. Accordingly, in keeping with our efforts to create bio-active heterocyclic compounds[xlvii-li] by means of metal catalysts, we have reported here the synthesis of a sequence of 2-aminoaryl benzimidazoles **3a–l** using an economical, effective bismuth catalyst in an environmentally beneficial manner.

2. EXPERIMENTAL

2.1. Material and Methods

General Information: $Bi(NO_3)_3 \cdot 5H_2O$ (98%), $Cu(OAc)_2 \cdot H_2O$ (98%), $Cd(NO_3) \cdot 5H_2O$ (98 %), $Fe(SO_4)_3$ (95 %), $Pb(NO_3)_2$ (98%), DMF, DMSO, EtOH, EtOAC, MeCN, , Cs_2CO_3 were purchased from Aldrich and exploited with no more purification. To find the melting points, the Cintex melting point apparatus was employed. A Brukner FT-IR spectrometer was used to obtain infrared (IR) spectra. $CDCl_3$/DMSO-d_6 was used to record the ^{1}H NMR and ^{13}C-NMR spectra using varian(400 MHz) spectrometer. To record the mass spectra, the Jeol SX-102 spectrometer was utilized.

General procedure for the synthesis of 6-Methyl-N-phenyl-1H-benzo[d]imidazol-2-amine (**3a**)**:**

One mmol (135 mg) of phenylisothiocyanate and one mmol (135 mg) of 4-methylbenzene-1,2-diamine are added gradually to solution of EtOH:H_2O (5 ml), and then one mmol (326 mg) of Cs_2CO_3 is added at room temperature. $Bi(NO_3)_3 \cdot 5H_2O$ (1 mmol, 485 mg) is added to the reaction mixture and stirred for several minutes at room temperature before the reaction is allowed to finish (monitored by TLC) and stirred for four hours at 100 °C. TLC is used to track the reaction's progress using a 1:1 ratio of ethyl acetate to hexane. The reaction mixture is cooled to room temperature once the reaction is finished. After that, the solution is five times cleaned using ethyl acetate (8 mL) and water (4 mL). The final product, 6-Methyl-N-phenyl-1H-benzo[d]imidazol-2-amine (**3a**), was obtained in 94 % yield by evaporating the organic layer and purifying the crude reaction mixture using silica gel (60-120 mesh) column chromatography.

6-Methyl-N-phenyl-1H-benzo[d]imidazol-2-amine (**3a**): mp 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.30-7.19 (m, 5H), 7.04-7.01 (m, 2H), 6.81 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.4, 135.3, 134.1, 132.7, 129.6, 127.0, 126.7, 115.3, 110.0, 20.3; FT-IR (KBr) 3279, 3061, 2866, 1612, 1584, 1548, 1498, 1462, 1336, 1243, 1119, 1067 cm^{-1}. m/z (ESI-MS) 224.11 $[M + H]^+$.

6-nitro-N-(4-nitrophenyl)-1H-benzo[d]imidazol-2-amine (**3b**): mp 186–180 ◦C; ^{1}H NMR (400 MHz, CDCl3) δ 7.73(d, J = 2.5 Hz, 1H), 7.5–7.45 (m, 2H), 7.16 (d, J = 9.9 Hz, 1H), 6.78 (br s, 1H), 6.45 (dd, J = 7.2, 2.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3 + DMSO-d6) δ 152.7, 151.5, 136.7, 133.5, 132.1, 130.8, 128.9, 127.3, 120.8, 114.2, 110.5; FT-IR (KBr) 3245, 3066, 2813, 1618, 1569, 1423, 1312, 1265, 1146, 1078, 1028cm^{-1} . m/z (ESI–MS) 300.14 [M + H]+.

6-methyl-N-p-tolyl-1H-benzo[d]imidazol-2-amine (**3c**): mp 143-144 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.41-7.36 (m, 3H), 7.31-7.14 (m, 3H), 6.87 (br s, 1H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 139.1, 138.4, 137.8, 133.8, 133.1, 131.3, 128.6, 118.8, 116.5, 112.5, 22.7, 20.4; FT-IR (KBr) 3255, 3212, 2918, 2846, 1619, 1579, 1449, 1407, 1378, 1256, 114955, 1009 cm^{-1}. m/z (ESI-MS) 238.28 $[M + H]^+$.

N-(2,4-dimethylphenyl)-1H-benzo[d]imidazol-2-amine (**3d**): mp 153–155 ◦C; ^{1}H NMR (400 MHz, CDCl3) δ 7.29–7.21 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.16–6.96 (m, 3H), 6.18 (br s, 1H), 2.38(s, 6H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 141.9, 136.4, 135.6, 134.7,

131.2, 129.9, 129.1, 127.3, 117.4, 114.5, 110.2, 25.5, 23.7; FT-IR (KBr) 3089, 2919, 2875, 2234, 1542, 1455, 1436, 1386, 1221, 1202, 1024 cm−1 . m/z (ESI–MS) 238.23 [M + H]+.

6-fluoro-N-(4-fluorophenyl)-1H-benzo[d]imidazol-2-amine (**3e**): mp 156–158 ◦C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.61 (t, J = 9.2 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 4.78 (br s, 1H), ^{13}C NMR (100 MHz, CDCl3 + DMSO-d6) δ 150.9, 142.9, 138.7, 134.5, 129.2, 128.6, 126.5, 126.3, 125.3, 121.6, 117.4, 20.1; FT-IR (KBr) 3066, 2946, 2142, 1656, 1534, 1433, 1365, 1355, 1235, 1215, 1050 cm^{-1} . m/z (ESI–MS) 246.09[M + H]+.

4,6-dimethyl-N-phenyl-1H-benzo[d]imidazol-2-amine (**3f**): mp 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.16-7.09 (m, 3H), 6.54 (br s, 1H), 2.52 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 134.7, 133.4, 132.6, 129.5, 129.1, 128.4, 128.7, 117.9, 115.59, 111.2, 23.9, 19.8; FT-IR (KBr) 3094, 2921, 2867, 2222, 1574, 1486, 1456, 1374, 1241, 1208, 1027 cm^{-1}. m/z (ESI-MS) 238.28 $[M + H]^{+}$.

6-methoxy-N-phenyl-1H-benzo[d]imidazol-2-amine (**3g**): mp 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 3H), 7.28-7.14 (m, 2H), 7.12-7.06 (m, 3H), 7.00 (br s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d6) δ 155.3, 152.9, 143.7, 134.5, 133.3, 130.9, 129.8, 129.3, 125.9, 123.6, 113.8, 54.19; FT-IR (KBr) 3345, 2962, 2857, 1577, 1545, 1516, 1329, 1264, 1238, 1192, 1131, 1075, 1033 cm^{-1}. m/z (ESI-MS) 240.21 $[M + H]^{+}$.

methyl 2-(4-cyanophenylamino)-3H-benzo[d]imidazole-5-carboxylate (**3h**): mp 214–216 ◦C; ^{1}H NMR (300 MHz, d6-DMSO, ppm) δ 7.96–7.67 (m, 3H), 6.93–6.81 (m, 5H), 6.83 (br s, 1H), 3.79 (s, 3H);^{13}C NMR (75 MHz, d6-DMSO) δ = 164.2, 151.2, 148.5, 143.1, 142.8, 136.2, 134.1, 129.5, 120.4, 118.5, 103.8, 101.2, 43.5; FT-IR (KBr) 3213, 3134, 2812, 1653, 1523, 1513, 1458, 1421, 1243, 1186, 1142, 1084, 1059, 1014 cm^{-1} . m/z (ESI-MS) 293.15 [M + H]+

2-(phenylamino)-3H-benzo[d]imidazole-5-carboxylic acid (**3i**): mp203–205ºC; ^{1}H NMR (400 MHz, CDCl3) δ 10.57 (s, 1H), 7.65 (s, 1H), 7.34–7.19(m, 3H), 7.45(d, J = 6.8 Hz, 2H), 7.12 (d, J = 7.2 Hz, 2H), 6.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.1, 133.9, 132.4, 129.9, 129.2, 128.5, 126.5, 113.0, 111.4, 109.0, 107.9; FT-IR (KBr) 3243, 3167, 1624, 1544, 1465, 1401, 1326, 1258, 1149, 1009, 917 cm−1 . m/z (ESI–MS) 293.15 [M + H]

6-fluoro-N-phenyl-1H-benzo[d]imidazol-2-amine (**3j**): mp 168–170 ◦C; ^{1}H NMR (400 MHz, CDCl3) δ 7.96–7.82 (m, 4H), 7.45(d, J = 7.6 Hz, 2H), 7.23 (d, J= 8.8 Hz, 2H), 4.78 (br s, 1H); ^{13}C NMR (100 MHz, CDCl3 + DMSO-d6) δ 154.41, 143.4, 138.7, 133.6, 130.5, 129.3, 128.4, 126.9, 122.9, 121.5, 116.9; FT-IR (KBr) 3087, 2983, 2132, 1634, 1512, 1456, 1356, 1321, 1223, 1211, 1045 cm^{-1} . m/z (ESI–MS) 215.07 [M + H].

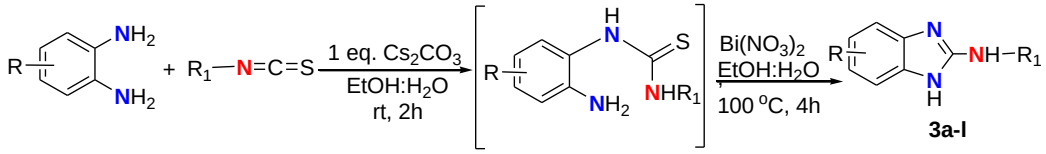
6-chloro-N-(4-chlorophenyl)-1H-benzo[d]imidazol-2-amine (**3k**): mp 164–166 ◦C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.48 (t, J = 9.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.21(d, J = 8.8 Hz, 1H), 4.89 (br s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl3 + DMSO-d6) δ 156.7, 148.5, 138.7, 133.7, 129.8, 127.9, 126.3, 125.1, 124.4, 119.0, 116.3, 20.1; FT-IR (KBr) 3069, 2965, 2134, 1656, 1523, 1443, 1386, 1345, 1267, 1235, 1030 cm^{-1} . m/z (ESI–MS) 278.11 [M + H]+.

2-(phenylamino)-3H-benzo[d]imidazole-5-carbonitrile (**3l**): mp 171–173 ◦C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.37–7.26(m, 3H), 7.25 (d, J = 6.8 Hz, 2H), 7.07 (d, J = 7.2 Hz, 2H), 6. 91 (br s, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 141.3, 139.5, 136.4 134.8, 132.6, 131.3, 128.6, 126.8, 113.9, 112.5, 109.0, 107.8; FT-IR (KBr) 3267, 3189, 1642, 1563, 1439, 1378, 1312, 1254, 1158, 1021, 932 cm^{-1} . m/z (ESI–MS) 235.13 [M + H]+.

3. RESULTS AND DISCUSSION

In the present work, 2-aminoarylbenzimidazoles were constructed from different *o*-phenylenediamines and phenylisothiocyanates through consecutive condensation/ nucleophilic substitution/*C-N* cross-coupling approach. *o*-phenylenediamine reacts with phenylisothiocyanate in EtOH:H_2Oat room temperature using cesium carbonate as base to

provide 1-(2-aminoaryl)-3-arylthioureaswhich further undergoes intra molecular *C-N* cross-coupling reaction to give target product 2-arylamino benzimidazoles **3a-l** in quantitative yield (Scheme 1).



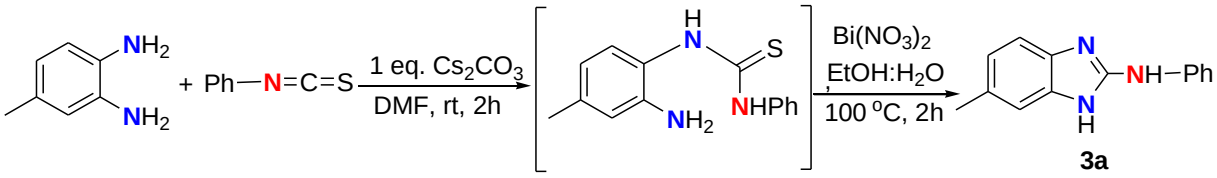
Scheme 1. Synthetic path for the construction of 2-aminoaryl Benzimidazoles.

To identify the optimized reaction conditions 4-methylbenzene-1,2-diamine and phenylisothiocyanate are chosen as model substrates, a range of solvents and metal sources were used at different temperatures. It is glad to observe that 1-(2-amino-4-methylphenyl)-3-phenylthiourea was achieved in quantitative conversion using Cs_2CO_3 as base and EtOH:H_2O as solvent at room temperature for 2h. Next, the 1-(2-amino-4-methylphenyl)-3-phenylthiourea on Bi catalyzed desulfurization and *C-N* coupling reaction afforded the target product (**3a**). The total findings of the entire investigation are compiled in Table 1. A controlled reaction utilizing 4-methylbenzene-1,2-diamine and phenyl- isothiocyanate in EtOH:H_2O without catalyst was performed in order to investigate the concert of catalyst; regrettably target product was not observed (Table 1, entry 1). Following a 10 hour reaction at 80 °C, only a 20% yield of the target product **1a** was observed (Table 1, entry 2). When the reaction was performed at room temperature for five hours with L-proline acting as the catalyst, the yield of the product increased to 60% (Table 1, entry 3). The reaction produced the desired product **3a** quantitatively 70 % yield in 2 hours at room temperature using $Bi(NO_3)_3.5H_2O$ as a catalyst, which is quite interesting (Table 1, entry 4). After that, the same conditions were followed for a 4-hour reaction with $Bi(NO_3)_3.5H_2O$ at 100 °C, yielding an 80% yield of the target product.

In the meantime, we conducted the reaction at room temperature using various percentage loadings of catalyst in EtOH in order to gain more insight into the amount of catalyst needed for the proficient conversion (Table 1, entries 11 and 13–15). The results of the experiment showed that within 4 hours, a 10 mol% load of the catalyst produced the wanted products with the utmost yield. The target product was produced in low yield by reducing the bismuth source quantity (5 mol percent) (Table 1, entry 15). The findings demonstrate that bismuth nitrate has a kindling effect as an accelerator, encouraging the timely and economical formation of the product. Furthermore, the reaction was accomplished in various solvents (Table 1, entries 4-11) to investigate the persuade of used solvents on the coupling of 4-methylbenzene-1,2-diamine with pheylisothiocyanate. The reaction was performed using the same catalyst, temperature and reaction time using different solvents like THF, EtOAc, CH_3CN, H_2O:EtOH, H_2O etc. Interestingly, the reaction in H_2O:EtOH produced the desired benzimidazole derivative in good yield (94 %), compared to other solvents.The experimental outcomes revealed that more polar and protic solvent like EtOH, EtOH: H_2O are appropriate solvents to afford the higher yields compared to aprotic solvents like THF, DMF, EtOAc and MeCN (Table 1).

Further, the evolution of the reaction was monitored by different catalysts such as $Cu(OAc)_2$, $Fe(SO_4)_3$, $Cd(NO_3)\cdot5H_2O$, $Pb(NO_3)_2$ were in H_2O:EtOH at 100 °C for 4-6 h (Table 1, entries 16-20). Comparing bismuth nitrate to other catalysts under study, it was discovered that it was a more effective catalyst for the synthesis of 2-arylaminobenzimidazoles. For the purpose of creating 2-aminoarylbenzimidazoles, the ideal reaction conditions were determined to be 10 mol% $Bi(NO_3)_3.5H_2O$ in the presence of H_2O:EtOH for two hours at 100 °C.

Table 1: Optimization of the reaction conditions for synthesis of 2-aminophenyl benzothiazole.[a]



3a

Entry	Catalyst	Solvent	Temp °C	Time (h)	Yield[b] (%)
1	-	DMF	rt	10h	-
2	-	DMF	80°C	10h	20%
3	L-Proline	DMF	rt	5h	60%
4	$Bi(NO_3)_3·5H_2O$	DMF	rt	2h	70%
5	$Bi(NO_3)_3·5H_2O$	DMF	100 °C	4h	80%
7	$Bi(NO_3)_3·5H_2O$	THF	100 °C	4h	77%
8	$Bi(NO_3)_3·5H_2O$	EtOAc	100 °C	4h	79%
9	$Bi(NO_3)_3·5H_2O$	MeCN	100 °C	4h	75%
10	$Bi(NO_3)_3·5H_2O$	EtOH	100 °C	4h	84%
11[a]	$Bi(NO_3)_3·5H_2O$	H_2O:EtOH	100 °C	4h	94%
12	$Bi(NO_3)_3·5H_2O$	H_2O	100 °C	4h	65%
13[c]	$Bi(NO_3)_3·5H_2O$	H_2O:EtOH	100 °C	4h	93%
14[d]	$Bi(NO_3)_3·5H_2O$	H_2O:EtOH	100 °C	4h	93%
15[e]	$Bi(NO_3)_3·5H_2O$	H_2O:EtOH	100 °C	4h	80%
16	$Cu(OAc)_2$	H_2O:EtOH	100 °C	4h	82%
17	$Fe(SO_4)_3$	H_2O:EtOH	100 °C	4h	80%
18	$Cd(NO_3)·5H_2O$	H_2O:EtOH	100 °C	4h	71%
19	$Cd(NO_3)·5H_2O$	H_2O:EtOH	100 °C	4h	75%
20	$Pb(NO_3)_2$	H_2O:EtOH	100 °C	6h	78%

[a] condition: 4methylPhenylenediamine (1 mmol), phenyl isothiocyanate (1 mmol), catalyst (20 mol%) and H_2O:EtOH (5 mL).
[b] Isolated yield.
[c] Catalyst loading Reaction: 15mol%.
[d] Catalyst loading: 10 mol%.
[e] Catalyst loading: 5 mol%

With the ideal reaction conditions in place, we looked more closely at the process's reach in relation to the other substrates (Figure 1). In a reaction with phenylisothiocyanate, *o*-phenylenediamine containing electron-releasing groups, such as 4-Me or 4-OMe, yielded the target products **3a** and **3g** in 94 % and 88 %. *o*-phenylenediamine with electron-withdrawing groups like 4-COOH and 4-CN caused reactions that resulted in the cross-coupled products **3i** and **3l** in yields of 70% and 68%, respectively. The target product **3j** is obtained in 76 % yield when *o*-phenylenediamine, which contains electronegative atoms like 4-F, reacts with phenyl isothiocyanate.

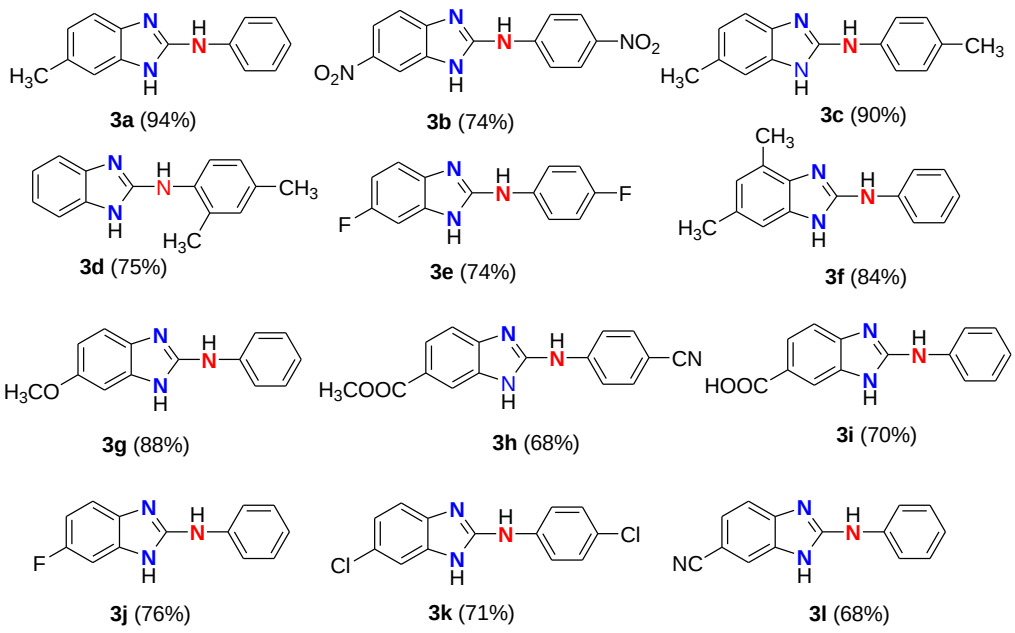
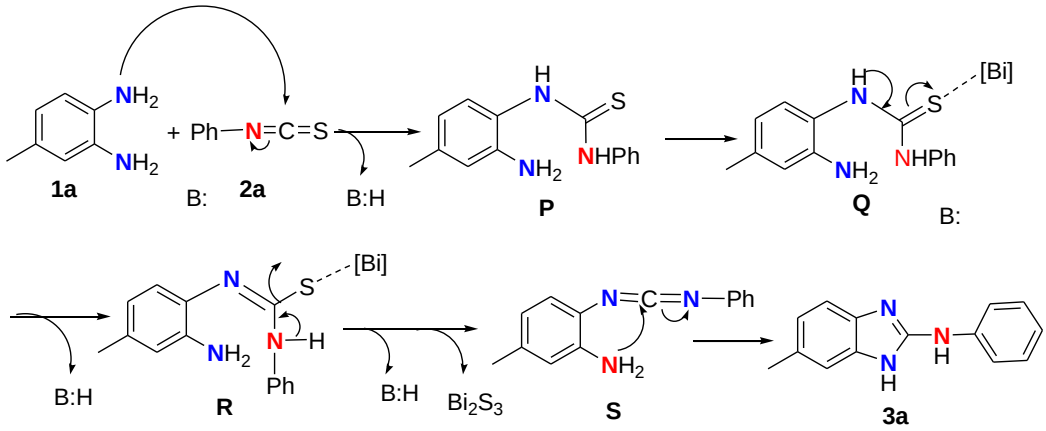


Figure 1. Substrate scope for the synthesis of 2-arylaminobenzimidazole.

Similar to this, under ideal circumstances, o-phenylenediamine holding disubstituted groups such as 2,4-DiMe carried out the reaction to yield product **3f** in an 84 % yield. Similarly, the reaction between *o*-phenylenediamine and phenylisothiocyanate bearing 2,4-diMe substituent's was easily completed, yielding the expected product **3d** in 75% of the cases. Additionally, o-phenylenediamine with 4-NO_2, 4-Me, 4-F, 4-$COOCH_3$, 4-Cl, substituents readily reacts with phenylisothiocyanate bearing 4-NO_2, 4-Me, 4-F, 4-CN, and 4-Cl to yield the expected products **3b**, **3c**, **3e**, **3h**, and **3k** in 68–90% yields. The aforementioned findings unequivocally demonstrate that the substrates with electron-releasing and electron-withdrawing groups are suitable for this procedure, resulting in a moderate to exceptional yields of substituted 2-aminoarylbenzimidazoles.

The suggested mechanism for final product 6-methyl-2-phenyl-1H-benzo[d]imidazole **3a** formation is presented in scheme 2 and is based on experimental evidence and literature reports[lii,liii]. Initially, the addition of 4-methylbenzene-1,2-diamine **1a** with pheylisothiocyanate **2a** generates 1-(2-amino-4-methylphenyl)-3-phenylthiourea intermediate (**P**). After that, the Bi(III) salt can synchronize with intermediate **P** to provide **Q**. Next, the deprotonation of **Q** intermediate, with base afford the intermediate **R** which on further deprotonation may provide 4-methyl-N1-((phenylimino)methylene)benzene-1,2-diamine (**S**) along with by-products Bi_2S_3*via* desulphurization. Next, the intermediate(**S**) on intramolecular *via C-N* cross coupling cyclization afford the 6-methyl-2-phenyl-1H-benzo[d]imidazole **3a** as product.



Scheme 2. Plausible mechanism.

4. CONCLUSION

Using an inexpensive, easily accessible bismuth catalyst, we have lucratively created a novel one-pot method for creating benzimidazole scaffolds by treating a range of *o*-phenylenediamines and phenyl isothiocyanates. The production of 2-aminoarylbenzimidazole derivatives in high yields was greatly aided by bismuth nitrate, a mild and effective green catalyst. Avoid using a lot of organic solvents; this protocol does not require column chromatography. Simple setup procedures, quick reaction times, effortless catalyst handling, and trouble-free product isolation with increased yields are the main drivers of the protocol that was carried out. As a result, this research encouraged future researchers to explore benzimidazole scaffolds in a cost-effective and eco-friendly manner.

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REFERENCES

i. a) Ansari K.F.; Lal C.; Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents; Eur. J. Med. Chem.; 2009, **44**, 2294-2299; (b) Bollikolla H.B.;Boddapati S.N.M.; Thangamani S.;Mutchu B.R.; Alam M.M.; Hussien M.; Jonnalagadda S.B.; Advances in synthesis and biological activities of benzotriazole analogues; A micro review; Journal of Heterocyclic Chemistry.; 2023, 60, 705-742; (c) Boddapati S.N.M.;Bollikolla H.B.; Bhavani K.G.; Saini H.S.; Ramesh N.; Jonnalagadda S.B.; Advances in synthesis and biological activities of quinazoline scaffold analogues; A review; Arabian Journal of Chemistry.; 2023,**16** (**10**),105190.

ii. Camacho J.; Barazarte, A.; Gamboa A.; *et al.;* Synthesis and biological evaluation of benzimidazole-5-carbohydrazide derivatives as antimalarial, cytotoxic and antitubercular agents; Bioorg. Med. Chem.; 2011, **19**, 2023-2029.

iii. Shin J.M.; Kim N.; Pharmacokinetics and pharmacodynamics of the proton pump inhibitors; Journal of Neurogastroenterology and Motility; 2013, **19**, 25–35.

iv. Wang X.J.; XiM.Y.; J.H. FuJ.H.; etal.; Synthesis, biological evaluation and SAR studies of benzimidazole derivatives as H1-antihistamine agents; Chin. Chem. Lett.; 2012, **23**, 707–710.

v. Arora R.K.; Kaur N.; Bansal Y.; Bansal G.; Novel coumarin–benzimidazole derivatives as antioxidants and safer anti-inflammatory agents; Acta Pharmaceutica.Sinica B.; 2014, **4**(**5**), 368–375.

vi. KusC.;Kilcigil G.A.;Ozbey S.; et al.; Synthesis and antioxidant properties of novel N-methyl-1,3,4-thiadiazol-2-amineand 4-methyl-2H-1,2,4-triazole-3(4H)-thione derivatives of benzimidazole class;Bioorg. Med. Chem.; 2008, **16**, 4294–4303.

vii. Raut C.N.;BharambeS.M.;Pawar Y.A.; Mahulikar P.P.; Microwave-mediated synthesis and antibacterial activity of some novel 2- (substituted biphenyl) benzimidazoles via Suzuki-Miyaura cross coupling reaction and their N-substituted derivatives; J. Heterocycl. Chem.; 2011, **48**, 419-425

viii. Kucukbaya H.; DurmazR.;Okyucu N.;Gunald S.; Antifungal activity of some bis-5-methylbenzimidazole compounds; Folia Microbiol.;2003,**48** (5), 679–681.

ix. Vinodkumar R.; Vaidya S.D.; Kumar B.V.S.; et al.; Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel Nsubstituted-2-(4-phenylethynyl-phenyl)-1H-benzimidazoles and N-substituted 2[4-(4,4-dimethyl-thiochroman-6-yl-ethynyl)-phenyl)-1H benzimidazoles; Eur. J. Med. Chem.; 2008, **43**, 986-995.

x. Bistrovic A.; Krstulovic L.; Harej A.; et al.; Design, synthesis and biological evaluation of novel benzimidazole amidines as potent multi-target inhibitors for the treatment of non-small cell lung cancer.*;* European Journal of Medicinal Chemistry;2018, **143**, 1616-1634.

xi. Craigo W.A.; Lesueur B.W.; Skibo E.B.; Design of highly active analogues of the pyrrolo[1,2-a]benzimidazole antitumor agents; J. Med. Chem.; 1999, **42**, 3324-3333.

xii. Wang X.J.; Yang M.L.; ZhangL.P.; etal.; Design of novel bis-benzimidazole derivatives as DNA minor groove binding agents; Chin. Chem. Lett.; 2014, **25**, 589–592.

xiii. Jain K.S.; Shah A.K.;BariwalJ.; et al.; Recent advances in proton pump inhibitors and management of acid-peptic disorders;Bioorg. Med. Chem.; 2007, **15**, 1181-1205.

xiv. Bansal Y.;Silakari O.; The therapeutic journey of benzimidazoles; A review, Bioorg. Med. Chem.; 2012, **20**, 6208-6236.

xv. Kumar B.; Rao P.; Synthesis and structural studies on transition metal complexes derived from 1-(2-thienyl)-1-ethanole-1H-benzimidazole; Asian J. Chem.; 2006, 18, 3060–3064. Molecules 2020, **25**, 1788.

xvi. DevivarR.V.; Kawashima E.; Revankar G.R.; Breitenbach J.M.; Kreske E.D.; Drach J.C.; Townsend L.B.; BenzimidazoleRibonucleosides. Design, Synthesis, and Antiviral Activity of Certain 2-(Alkylthio)-and 2-(Benzylthio)-5, 6-dichloro-1-(beta.-D-ribofuranosyl) benzimidazoles; J. Med. Chem.; 1994, 37, 2942–2949.

xvii. Ansari K.; Lal C.; Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents; Eur. J. Med. Chem.; 2009, **44**, 2294–2299.

xviii. KatiyarA.; Rai J.; Gangwar S.; Mohanty A.K.; MishraA.P.; Biological Activities of Substituted Benzimidazole Derivatives; J. Drug Discov. Dev.; 2018, **2**, 2–10.

xix. White A.W.; Almassy R.; Calvert A.H.; Curtin N.J.; Griffin R.J.; Hostomsky Z.; Maegley K.; Newell D.R.; Srinivasan S.; Golding B.T.; Resistance-modifying agents, Synthesis and biological properties of benzimidazole inhibitors of the DNA repair enzyme poly (ADP-ribose) polymerase; J. Med. Chem.; 2000, **43**, 4084–4097.

xx. Shrivastava N.; Naim M.J.; Alam M.J.; Nawaz F.; Ahmed S.; Alam O.; Benzimidazole scaffold as anticancer agent: synthetic approaches and structureeactivity relationship. Arch Pharmazie.; 2017, **350**, e201700040.

xxi. Shimomura I.; Yokoi A.;Kohama I.;Kumazaki M.; Tada Y.; Tatsumi K.; et al.; Drug library screen reveals benzimidazole derivatives as selective cytotoxic agents for KRAS-mutant lung cancer; Cancer Lett.; 2019, **451**,11e22

xxii. Hauel N.H.; Nar H.; Priepke H.; Ries U.; Stassen J.M.; Wienen W.; Structure-based design of novel potent nonpeptide thrombin inhibitors; J. Med. Chem.; 2002, **45**, 1757–1766.

xxiii. Zornik D.; Meudtner R.M.; MalahEl.T.; Thiele C.M.; Hecht S.; Designing Structural Motifs for Clickamers: Exploiting the 1, 2, 3-Triazole Moiety to Generate Conformationally Restricted Molecular Architectures; Chem. A Eur. J.; 2011, **17**, 1473–1484.

xxiv. Lim H.J.; MyungD.; Lee I.Y.C.; Jung M.H.; Microwave-assisted synthesis of benzimidazoles, benzoxazoles, and benzothiazoles from resin-bound esters; J. Comb. Chem.; 2008, **10**, 501–503.

xxv. WuZ.; Rea P.; Wickham G.; One-pot'nitro reduction–cyclisation solid phase route to benzimidazoles; Tetrahedron Lett.; 2000, **41**, 9871–9874.

xxvi. Benincori T.; Sannicolo F.; New benzimidazole synthesis; J. Heterocycl. Chem.; 1988, **25**, 1029–1033.

xxvii. Yang D.; Fokas D.; Li J.; Yu L.; Baldino C.M.; A versatile method for the synthesis of benzimidazoles from o-nitroanilines and aldehydes in one step via a reductive cyclization; Synthesis, 2005,**2005**, 47–56.

xxviii. Chemler S.R.; Fuller P.H.; Heterocycle synthesis by copper facilitated addition of heteroatoms to alkenes, alkynes and arenes; Chem. Soc. Rev.; 2007, **36**, 1153–1160.

xxix. Ma D.; Cai Q.; Copper/amino acid catalyzed cross-couplings of aryl and vinyl halides with nucleophiles; Acc. Chem. Res.; 2008, **41**, 1450–1460.

xxx. EvindarG.; Batey R.A.; Copper-and palladium-catalyzed intramolecular aryl guanidinylation: An efficient method for the synthesis of 2-aminobenzimidazoles; Org. Lett.; 2003, **5**, 133–136.

xxxi. ZhengN.; Buchwald S.L.; Copper-catalyzed regiospecific synthesis of N-alkylbenzimidazoles; Org. Lett.; 2007, **9**, 4749–4751.

xxxii. Yuan Q.; Ma D.; A one-pot coupling/hydrolysis/condensation process to pyrrolo [1–a] quinoxaline; J. Organ. Chem.; 2008, **73**, 5159–5162.

xxxiii. Chen Y.; Xie X.; Ma D.; Facile access to polysubstituted indoles via a cascade Cu-catalyzed arylation− condensation process; J. Organ. Chem.; 2007, **72**, 9329–9334.

xxxiv. Wang B.; Lu B.; Jiang Y.; Zhang Y.; Ma D.; Assembly of isoquinolines via CuI-catalyzed coupling of β-Keto esters and 2-halobenzylamines; Org. Lett.; 2008, **10**, 2761–2763.

xxxv. Chen Y.; Wang Y.; Sun Z.; Ma D.; Elaboration of 2-(Trifluoromethyl) indoles via a cascade coupling/condensation/deacylation Process; Org. Lett.; 2008, **10**, 625–628.

xxxvi. Evindar G.; Batey R.A.; Parallel synthesis of a library of benzoxazoles and benzothiazoles using ligand-accelerated copper-catalyzed cyclizations of ortho-halobenzanilides; J. Organ. Chem.; 2006, **71**, 1802–1808.

xxxvii. Kondraganti L.; ManaboluS.b.; Dittakavi R.; Synthesis of Benzimidazoles via Domino Intra and Intermolecular C-N Cross-Coupling Reaction; Chem. Sel.; 2018, **3**, 11744–11748.

xxxviii. BoddapatiS.N.M.;Tamminana R.; Gollapudi R.K.;Nurbasha S.; Assal M.E.; Alduhaish O.; Siddiqui M.R.H.;BollikollaH.B.;Adil S.F.; Copper-Promoted One-Pot Approach: Synthesis of Benzimidazoles. Molecules; 2020, **25**(8),1788.

xxxix. Bothwell J.M.;Krabbez S.W.; Mohan R.S.; Applications of bismuth (III) compounds in organic synthesis; Chem. Soc. Rev.; 2011, **40**, 4649-4707.

xl. BadgujarD.M.;Talawar M.B.; Asthana S.N.; et al.; Microwave assisted facile synthesis of {1/1,3-bis/1,3,5-tris-[(2- nitroxyethylnitramino)-2,4,6-trinitrobenzene]} using

bismuth nitrate pentahydrate as an eco-friendly nitrating agent; J. Hazard. Mater.; 2008, **152**, 820-825.

xli. Badgujar D.M.; Talawar M.B.; Asthana S.N.; MahulikarP.P.; Synthesis and characterization of methyl nitramino-2,4,6-trinitobenzenes using bismuth nitrate pentahydrate as an eco-friendly nitrating agent; J. Sci. Ind. Res.; 2010, **69**, 208-210.

xlii. Cunha S.; de Lima B.R.; de Souza A.R.; Bismuth nitrate pentahydrate: a new and environmentally benign reagent for guanidylation of Nbenzoylthioureas; Tetrahedron Lett.; 2002, **43**, 49-52.

xliii. Banik B.K.; BanikI.;Renteriaa M.; Dasgupta S.K.; A straightforward highly efficient Paal–Knorr synthesis of pyrroles; Tetrahedron Lett.; 2005, **46**, 2643-2645.

xliv. KhodaeiM.M.;Khosropour A.R.;Beygzadeh M.; An efficient and environmentally friendly method for synthesis of 3,4-Dihydropyrimidin-2(1H)-ones catalyzed by Bi(NO3)3.5H2O; Synth. Commun.; 2004, **34**, 1551-1557.

xlv. Alexander V.M.; Bhat R.P.; Samant S.D.; Bismuth (III) nitrate pentahydrate a mild and inexpensive reagent for synthesis of coumarins under mild conditions; Tetrahedron Lett.; 2005, **46**, 6957-6959.

xlvi. Aggen D.H.; Arnold J.N.; Hayes P.D.; Smoter N.J.; MohanR.S.; Bismuth compounds in organic synthesis. Bismuth nitrate catalyzed chemoselective synthesis of acylals from aromatic aldehydes; Tetrahedron; 2004, **60**, 3675-3679.

xlvii. S N Murthy B.; Mujahid Alam M.; Ramana T.; Hari Babu B.; Efficient Pd(II)-Catalyzed Regioselective Ortho-halogenation of Arylcyanamide at Mild-Temperature; New Journal of chemistry; 2021, **45**, 17176-17182.

xlviii. S N MurthyB.; Mohan K.C.; RamanaM.B.; Ramana T.; Hari Babu B.; Copper-catalyzed synthesis of 2-aminophenyl benzothiazoles; A novel approach. Organic & Bio molecular Chemistry; 2018, **16**, 8267-8272.

xlix. S N Murthy B.; Naresh P.; Ramana M.B.; Hari Babu, B.; The synthesis of arylcyanamides: a copper-catalyzed consecutive desulfurization and C–N cross-coupling strategy; New Journal of chemistry; 2018, **42**, 918-922.

l. S N Murthy B.; Jagan Mohana Rao S.; Baby Ramana M.; Hari Babu B.; Syed Farooq Adil.; Mujeeb Khan; Synthesis of Substituted 2-aminobenzoxazoles and 2,5-disubstituted Tetrazole amines using copper promoted desulfurization and C-N cross coupling strategies; Arabian Journal of Chemistry; 2020, **13**(2), 4477-4494.

li. J M Rao S.; S N Murthy B.; Raghuram M.; Farooq Adil S.; Mohammed Rafi S.; Alduhaish O.; Siddiqui, M.R.H.; Hari Babu, B.; $Pd(PPh_3)_4$ Catalyzed Synthesis Of Indazole Derivatives as Potent Anti-Cancer Drug; Applied Sciences; 2020, **10**, 3792.

lii. Duangkamol C.; Wong Phakhodee W.; Pattarawarapan M.; Potassium Periodate Mediated Oxidative Cyclodesulfurization toward Benzofused Nitrogen Heterocycles; Synthesis; 2020, **52**, 1981-1990.

liii. Cunha S.; Manoel T.; Rodrigues Jr.; The first bismuth(III)-catalyzed guanylation of thioureas;*Tetrahedron Letters.;* 2006, **47**, 6955-6956.

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