CARO'S ACID-SILICA GEL CATALYZED SYNTHESIS OF 2-ARYL-1H-BENZIMIDAZOLES AND 2-ARYL-1-ARYLMETHYL-1H-BENZIMIDAZOLES

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Abstract – An efficient procedure for the synthesis of 2-aryl-1H-benzimidazoles and 2-aryl-1-arylmethyl-1H-benzimidazoles has been developed by simple condensation of o-phenylenediamine and aromatic aldehyde in the presence of Caro’s acid supported on silica gel in ethanol under reflux.

Structures containing benzimidazole have been well documented to exhibit a wide range of biological properties. This class of molecules has been found for application in several therapeutic areas such as antiparasitic,1 antifungal, antihypertensive, antitumor,2 antimicrobial,3 anti-inflammatory,4 and antiviral activities.5 Furthermore, these compounds exhibit significant activity against several viruses such as HIV,6 herpes (HSV-1),7 RNA,8 influenza,9 and human cytomegalovirus.10 Because of intense interest in the biological activity of these compounds, in recent years, several synthetic procedures for preparing benzimidazoles have been reported including classical conditions with microwave irradiation11 and by using Lewis acids such as Sc(OTf)3,12 Yb(OTf)3,13 In(OTf)3,14 oxalic acid,15 proline,16 H2O2/HCl,17 and p-toluenesulfonic acid-silica gel.18 Recently, the use of Caro’s acid -
silica gel (CA-SiO2) as catalysts or promoters in organic synthesis has attracted great interest from many chemists. CA-SiO2 can enhance the reactivity and selectivity of many types of reaction, such as oxidative coupling of thiols to disulfides, conversion of thioamides into amides, carbonyl compounds from oximes.

In connection with our ongoing work on synthesis of heterocyclic compounds, we now wish to report a facile procedure for the preparation of benzimidazoles derivatives with CA-SiO2 as a nontoxic, inexpensive, and easily available reagent. We have found that when a mixture of 1a and 2a was stirred at reflux for 2.5 h in 96% EtOH in the presence of CA-SiO2 (0.2 g), 1-benzyl-2-phenyl-1H-benzimidazole 4a was isolated in 90% yield (until the o-phenylenediamine disappeared, as shown by TLC) (Scheme 1) at reflux for 2.5 h. The proposed mechanism for synthesis of the 2-arylbenzimidazoles and 2-aryl-1-arylmethyl-1H-benzimidazoles in the presence of CA-SiO2 may tentatively be visualized to occur via a tandem sequence of reactions as depicted in Scheme 2, the mechanism of reaction can be considered to proceed via the initial formation of the imine (5) from o-phenylenediamine with an aromatic aldehyde, and the present reaction can be considered through two separate approaches which end in the different result.

When the R2 is electron-withdrawing, (Table 1, entry j), the imine (5) is cyclized to lead to the corresponding benzimidazoline (6) under the influence of CA-SiO2 and a subsequent oxidation of 6 affords the benzimidazole (3). On the other hand, when the R2 is electron-releasing and hydrogen (Table 1, entries a-h), the aromatic aldehyde also attacks the another amine to form an intermediate N,N-dibenzylidene-o-phenylenediamine (7) and via protonation and cyclization the intermediate (8) forms, further deprotonation and 1,3-hydrid transfer afford the 1-benzyl-2-phenyl-1H-benzimidazole (4). When R2 is p-chlorophenyl group, 3i and 4i form, because chlorine atom is both electron-releasing and electron-withdrawing (Table 1, entry i).
Thus, we have found that the aromatic aldehyde plays a major role in the selectivity of the products. In summary, we have described a mild, convenient method for the preparation of 2-arylbenzimidazoles and 2-aryl-1-arylmethyl-1H-benzimidazoles by condensation of o-phenylenediamine and aromatic aldehydes using cheap, non-toxic, and easily available CA-SiO2 heterogeneous catalyst.

**Table 1.** Synthesis of 2-arylbenzimidazoles and 2-aryl-1-arylmethyl-1H-benzimidazoles in the presence of CA-SiO2 under reflux

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Time(h)</th>
<th>Mp(°C) Found</th>
<th>Mp(°C) Reported</th>
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<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>C6H5</td>
<td>0</td>
<td>90</td>
<td>2.5</td>
<td>133-5</td>
<td>134-26</td>
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<tr>
<td>b</td>
<td>H</td>
<td>2-MeOC6H4</td>
<td>0</td>
<td>81</td>
<td>2.15</td>
<td>151-3</td>
<td>151-27</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>4-MeOC6H4</td>
<td>0</td>
<td>83</td>
<td>2.15</td>
<td>129-31</td>
<td>129-30-28</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>4-MeC6H4</td>
<td>0</td>
<td>82</td>
<td>2.5</td>
<td>125-7</td>
<td>127-28-29</td>
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<tr>
<td>e</td>
<td>H</td>
<td>4-Me2NC6H4</td>
<td>0</td>
<td>74</td>
<td>2.5</td>
<td>152-5</td>
<td>255-28</td>
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<tr>
<td>f</td>
<td>Me</td>
<td>C6H5</td>
<td>0</td>
<td>91</td>
<td>2.15</td>
<td>184-6</td>
<td>-28</td>
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<tr>
<td>g</td>
<td>Me</td>
<td>4-MeOC6H4</td>
<td>0</td>
<td>92</td>
<td>2.15</td>
<td>180-1</td>
<td>-</td>
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<tr>
<td>h</td>
<td>Me</td>
<td>4-MeC6H4</td>
<td>0</td>
<td>89</td>
<td>2.5</td>
<td>175-7</td>
<td>177-30</td>
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<tr>
<td>i</td>
<td>H</td>
<td>4-ClC6H4</td>
<td>65</td>
<td>30</td>
<td>3</td>
<td>300-236</td>
<td>301-30</td>
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<tr>
<td>j</td>
<td>H</td>
<td>4-NO2C6H4</td>
<td>89</td>
<td>0</td>
<td>2.5</td>
<td>305-7</td>
<td>306-831</td>
</tr>
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</table>

#Reaction conditions: o-phenylenediamine (1 mmol), aldehyde (2.1 mmol), CA-SiO2 (0.2 g), and 96% EtOH (5 mL), reflux. #Isolated yields. #The residue was chromatographed on silica gel(AcOEt:hexane=1:1) to give 3i and 4i. #Mp is for 3i.
EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were determined on Bruker 300 DRX Avance instrument at 300 and 75MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

**General procedure:** A mixture of the appropriate aldehyde (2.1 mmol), o-phenylenediamine (1 mmol), CA-SiO$_2$ (0.2 g), and 96% EtOH (5 mL) was heated with stirring at reflux for the time period as indicated in Table 1. After completion of the reaction (TLC, AcOEt / n-hexane, 1/1), the crude product was recrystallized from EtOH.

**General procedure for the preparation of catalyst:** To ice cooled 98% sulfuric acid (4.7 g) is added in small portions potassium persulfate (4.5 g) with stirring; to this are added crushed ice (13 g) and water (4 g) and the temperature is kept below 15 °C. Silica gel (5 g, TLC grade, Kieselgel 60 G, particle size 15µm) is added in portions to the mixture and the mixture was stirred for 4 h in ice-water bath. The mixture is then filtered under suction and dried in a desiccator to give a white free flowing powder.$^{19}$

1-Benzyl-5,6-dimethyl-2-phenyl-1$^H$-benzimidazole (4f): IR (KBr), $\nu_{\text{max}}$ 3050, 2830, 1623 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$H: 2.34(s, 3H, CH$_3$), 2.40(s, 3H, CH$_3$), 5.43(s, 2H, CH$_2$), 7.00-7.66(m, 12H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$C:19.83 (CH$_3$), 20.10 (CH$_3$), 47.79 (CH$_2$), 110.10, 119.41, 125.40, 127.18, 128.20, 128.56, 128.69, 129.24, 129.61, 131.22, 131.87, 134.10, 136.14, 141.00, 152.77; MS (m/z, %): 312 (M$^+$, 100), 298 (25), 235 (25), 221 (80), 207 (50), 165 (25), 118 (50), 77 (30), 65 (30). *Anal. Caled for C$_{24}$H$_{24}$N$_2$: C, 84.67; H, 7.11; N, 8.23. Found: C, 84.56; H, 7.02; N, 8.13.*

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-5,6-dimethyl-1$^H$-benzimidazole (4g): IR (KBr), $\nu_{\text{max}}$ 3045, 2930, 1605 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$H: 2.34(s, 3H, CH$_3$), 2.39(s, 3H, CH$_3$), 3.81(s, 3H, CH$_3$), 3.86(s, 3H, CH$_3$), 5.39(s, 2H, CH$_2$), 6.87-7.26(m, 10H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$C:19.83 (CH$_3$), 20.10 (CH$_3$), 47.24 (CH$_2$), 54.79 (OCH$_3$), 54.85 (OCH$_3$), 110.01, 113.60, 113.89, 119.23, 122.13, 126.61, 128.26, 130.08, 130.89, 131.40, 134.15, 141.135, 152.76, 158.50, 150.20; MS (m/z, %): 372 (M$^+$, 95), 252 (95), 238 (50), 221 (25), 208 (35), 135 (35), 121 (100), 91 (60), 77 (30), 65 (15). *Anal. Caled for C$_{24}$H$_{24}$N$_2$O$_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.25; H, 6.32; N, 7.43.*

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REFERENCES


