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

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Abstract – An efficient procedure for the synthesis of 2-aryl-1*H*-benzimidazoles and 2-aryl-1-arylmethyl-1*H*-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.

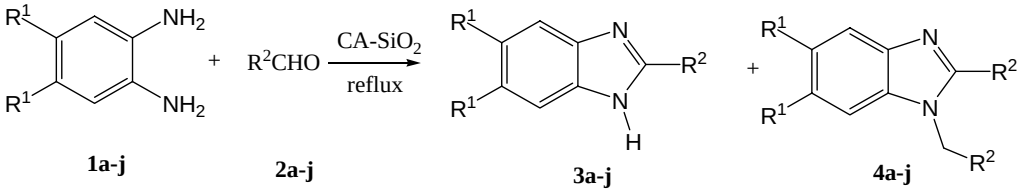
Structures containing benzimidazole have been well documented to exhibit a wide range of biological properties. This class of molecules has been found for application in several therapeutic areas such as antiparasitic,[1] antifungal, antihypertensive, antitumor,[2] antimicrobial,[3] anti-inflammatory,[4] 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 irradiation[11] and by using Lewis acids such as $Sc(OTf)_3$,[12] $Yb(OTf)_3$,[13] $In(OTf)_3$,[14] oxalic acid,[15] proline,[16] H_2O_2/HCl,[17] and *p*-toluenesulfonic acid-silica gel.[18] Recently, the use of Caro's acid -

silica gel (CA-SiO_2) as catalysts or promoters in organic synthesis has attracted great interest from many chemists. CA-SiO_2 can enhance the reactivity and selectivity of many types of reaction, such as oxidative coupling of thiols to disulfides,[19] conversion of thioamides into amides,[20] carbonyl compounds from oximes.[21]

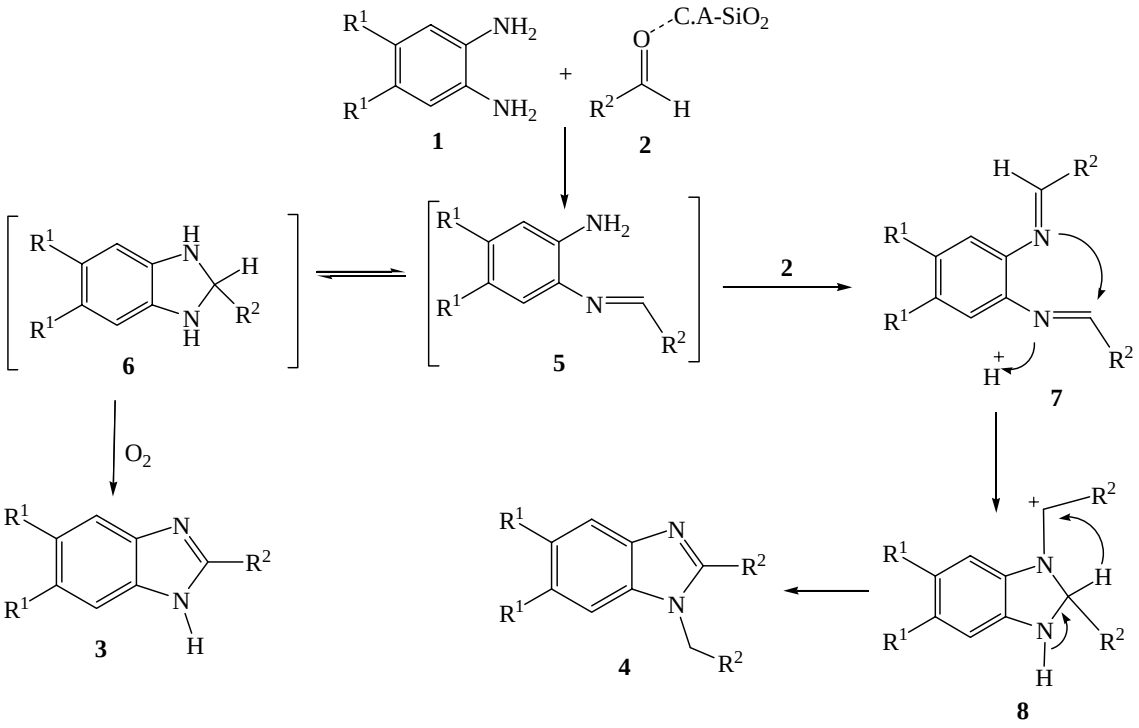
In connection with our ongoing work on synthesis of heterocyclic compounds,[22-25] we now wish to report a facile procedure for the preparation of benzimidazoles derivatives with CA-SiO_2 as a nontoxic, inexpensive, and easily available reagent. We have found that when a mixture of **1a** and **2a** was stirred at reflux for 2.5 h in 96% EtOH in the presence of CA-SiO_2 (0.2 g), 1-benzyl-2-phenyl-1*H*-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-1*H*-benzimidazoles in the presence of CA-SiO_2 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.



1a-j **2a-j** **3a-j** **4a-j**

Scheme 1

When the R^2 is electron-withdrawing, (Table 1, entry j), the imine **(5)** is cyclized to lead to the corresponding benzimidazoline **(6)** under the influence of CA-SiO_2 and a subsequent oxidation of **6** affords the benzimidazole **(3)**. On the other hand, when the R^2 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-1*H*-benzimidazole **(4)**. When R^2 is *p*-chlorophenyl group, **3i** and **4i** form, because chlorine atom is both electron-releasing and electron-withdrawing (Table 1, entry i).



Scheme 2

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-1*H*-benzimidazoles by condensation of *o*-phenylenediamine and aromatic aldehydes using cheap, non-toxic, and easily available CA-SiO_2 heterogeneous catalyst.

Table 1. Synthesis of 2-arylbenzimidazoles and 2-aryl-1-arylmethyl-1*H*-benzimidazoles in the presence of CA-SiO_2 under reflux[a]

Entry	R^1	R^2	Yield (%)[b] **3a-j**	Yield (%)[b] **4a-j**	Time(h)	Mp(°C) Found	Mp(°C) Reported
a	H	C_6H_5	0	90	2.5	133-5	134 [26]
b	H	2-$MeOC_6H_4$	0	81	2.15	151-3	151[27]
c	H	4-$MeOC_6H_4$	0	83	2.15	129-31	129-30 [28]
d	H	4-MeC_6H_4	0	82	2.5	125-7	127-28 [29]
e	H	4-$Me_2NC_6H_4$	0	74	2.5	152-5	255 [28]
f	Me	C_6H_5	0	91	2.15	184-6	-[16]
g	Me	4-$MeOC_6H_4$	0	92	2.15	180-1	-
h	Me	4-MeC_6H_4	0	89	2.5	175-7	177 [30]
i[c]	H	4-ClC_6H_4	65	30	3	300-2[d]	301[30]
j	H	4-$NO_2C_6H_4$	89	0	2.5	305-7	306-8[31]

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), aldehyde (2.1 mmol), CA-SiO_2 (0.2 g), and 96% EtOH (5 mL), reflux. [b]Isolated yields. [c]The residue was chromatographed on silica gel(AcOEt:hexane=1:1) to give **3i** and **4i**. [d]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 Heracus 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 recystallized 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 l5 °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), ν_{max} 3050, 2830, 1623 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_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 ($CDCl_3$) δ_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), 91 (80), 77 (30), 65 (30). *Anal*. Calcd 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), ν_{max} 3045, 2930, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_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 ($CDCl_3$) δ_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, 160.20; 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*. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.25; H, 6.32; N, 7.43.

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