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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.

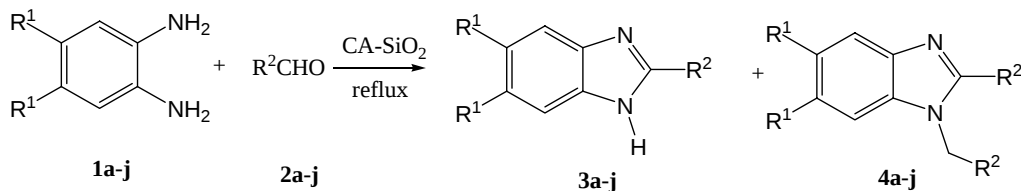
Structures containing benzimidazole have been well documented to exhibit a wide range of biological properties. This class of molecules has been found for application in several therapeutic areas such as antiparasitic,¹ antifungal, antihypertensive, antitumor,² antimicrobial,³ anti-inflammatory,⁴ and 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 -

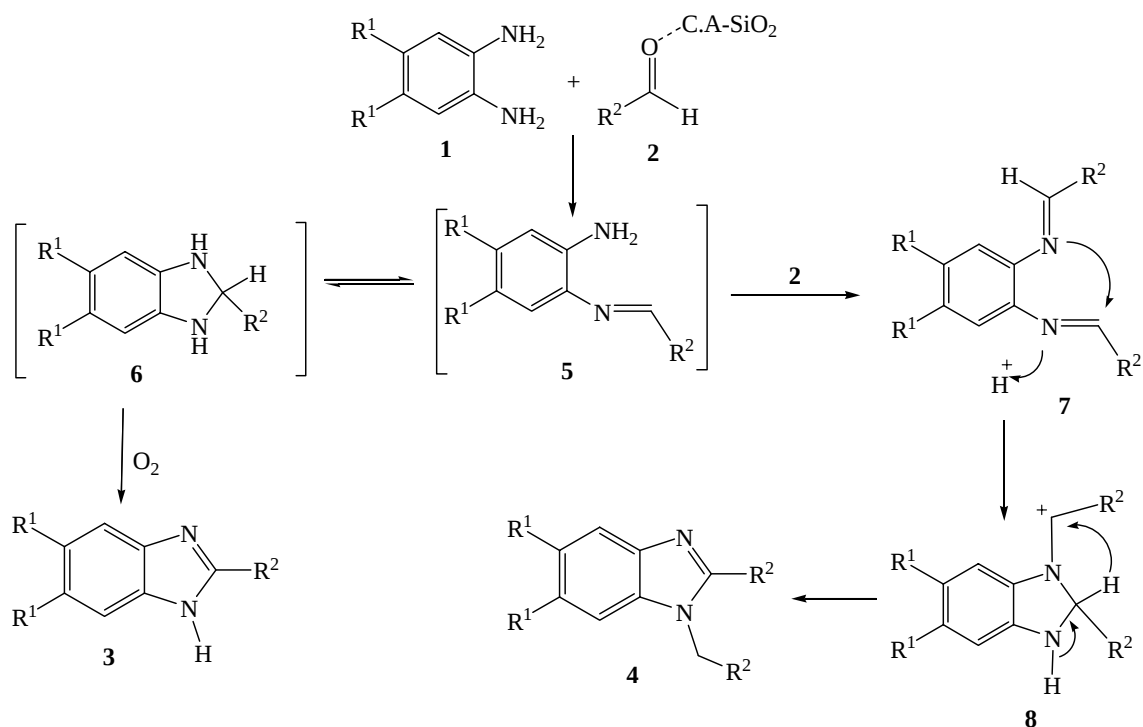
silica gel (CA-SiO₂) as catalysts or promoters in organic synthesis has attracted great interest from many chemists. CA-SiO₂ can enhance the reactivity and selectivity of many types of reaction, such as oxidative coupling of thiols to disulfides,¹⁹ conversion of thioamides into amides,²⁰ carbonyl compounds 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-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-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-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.



Scheme 1

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-1*H*-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).



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-SiO₂ heterogeneous catalyst.

Table 1. Synthesis of 2-arylbenzimidazoles and 2-aryl-1-arylmethyl-1*H*-benzimidazoles in the presence of CA-SiO₂ 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 ₆ H ₅	0	90	2.5	133-5	134 ²⁶
b	H	2-MeOC ₆ H ₄	0	81	2.15	151-3	151 ²⁷
c	H	4-MeOC ₆ H ₄	0	83	2.15	129-31	129-30 ²⁸
d	H	4-MeC ₆ H ₄	0	82	2.5	125-7	127-28 ²⁹
e	H	4-Me ₂ NC ₆ H ₄	0	74	2.5	152-5	255 ²⁸
f	Me	C ₆ H ₅	0	91	2.15	184-6	- ¹⁶
g	Me	4-MeOC ₆ H ₄	0	92	2.15	180-1	-
h	Me	4-MeC ₆ H ₄	0	89	2.5	175-7	177 ³⁰
i ^c	H	4-ClC ₆ H ₄	65	30	3	300-2 ^d	301 ³⁰
j	H	4-NO ₂ C ₆ H ₄	89	0	2.5	305-7	306-8 ³¹

^aReaction conditions: *o*-phenylenediamine (1 mmol), aldehyde (2.1 mmol), CA-SiO₂ (0.2 g), and 96% EtOH (5 mL), reflux. ^bIsolated yields. ^cThe residue was chromatographed on silica gel(AcOEt:hexane=1:1) to give **3i** and **4i**. ^dMp 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. ^1H 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-SiO₂ (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), ν_{max} 3050, 2830, 1623 cm⁻¹; ^1H NMR (CDCl₃) δ_{H} : 2.34(s, 3H, CH₃), 2.40(s, 3H, CH₃), 5.43(s, 2H, CH₂), 7.00-7.66(m, 12H, ArH); ^{13}C NMR (CDCl₃) δ_{C} : 19.83 (CH₃), 20.10 (CH₃), 47.79 (CH₂), 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 C₂₄H₂₄N₂: 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; ^1H NMR (CDCl₃) δ_{H} : 2.34(s, 3H, CH₃), 2.39(s, 3H, CH₃), 3.81(s, 3H, CH₃), 3.86(s, 3H, CH₃), 5.39(s, 2H, CH₂), 6.87-7.26(m, 10H, ArH); ^{13}C NMR (CDCl₃) δ_{C} : 19.83 (CH₃), 20.10 (CH₃), 47.24 (CH₂), 54.79 (OCH₃), 54.85 (OCH₃), 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 C₂₄H₂₄N₂O₂: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.25; H, 6.32; N, 7.43.

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