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IMPROVED CONVENIENT AND ENVIRONMENTALLY BENIGN SYNTHESIS OF BIOLOGICAL ACTIVE BENZIMIDAZOLES USING ACTIVATED CARBON AND MOLECULAR OXYGEN

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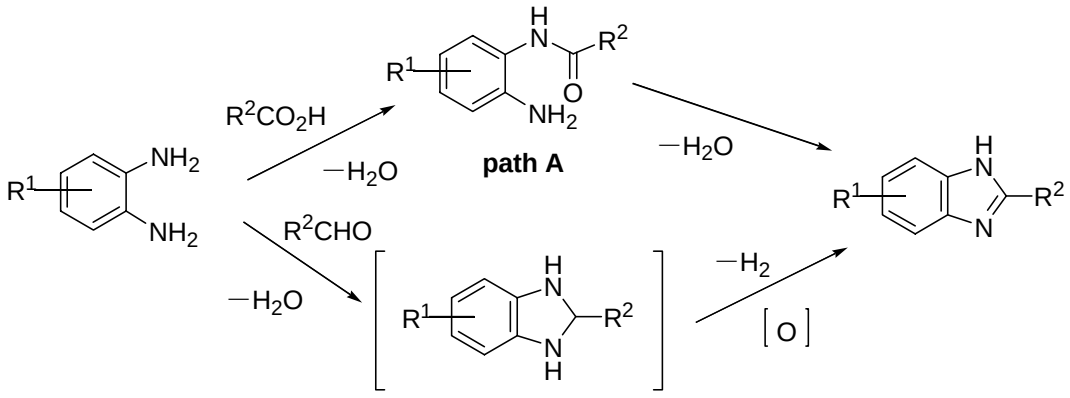
Abstract - The reaction of 1,2-phenylenediamine with a variety of aromatic aldehydes in xylenes gave the corresponding benzimidazole derivatives in good to excellent yields (82-93%) in the presence of dry activated carbon and bubbling molecular oxygen. The present reaction involves the simple procedure, easy workup and environmentally benign materials such as molecular oxygen and reusable activated carbon.

Benzimidazole derivatives have been used in human therapeutic areas as antiulcers, antihypertensives, antivirals, antifungals or anticancers and in veterinarian medicine as anthelmintic.[1] They are regarded as 'privileged sub-structures' for drug design by medicinal chemists.[2] Accordingly developing a simple and efficient methodology to prepare benzimidazole derivatives in preparative-scale, taking environmental issues into consideration, would be of great significance. As a part of the study of developing such a methodology, this paper deals with reaction of 1,2-phenylenediamine with aromatic aldehyde in the presence of activated carbon and molecular oxygen.

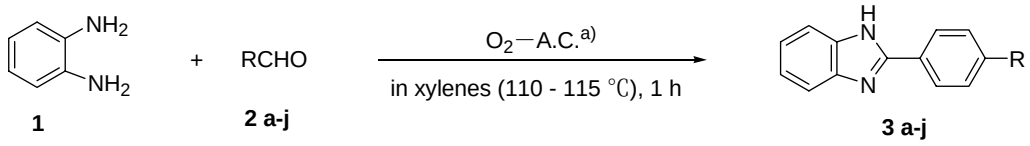
While many strategies are available for benzimidazole synthesis,[2] the most popular approaches generally involve condensation-dehydration of 1,2-phenylenediamine with carboxylic acids (or equivalents) (path A), or condensation with aldehydes under oxidative conditions (path B) (Scheme 1).



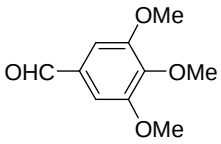
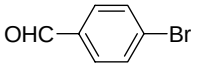
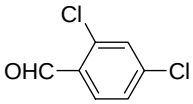
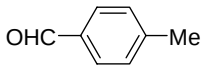
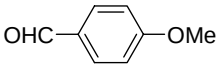
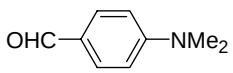
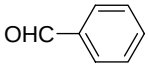
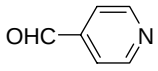
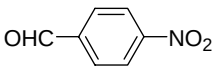
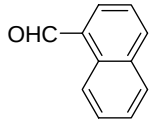
Scheme 1

The reaction with R^2CO_2H (path A) requires generally the harsh reaction conditions and proceeds stepwise via intermediate amide, on the other hand extensive structural diversity is available commercially in the reaction with aldehydes (path B) and the reaction proceeds through a benzimidazoline, which requires an oxidative step for conversion to benzimidazole. Recently, it was reported that the reaction of 1,2-phenylenediamine with benzaldehyde in the presence of activated carbon and molecular oxygen gave 2-phenylbenzimidazole in 64% yield.[3] However, the only reaction resulted in a long reaction time (26 h) and relatively low yield (64%). So, it is commenced to evolve and improve this reaction to find much better reaction conditions and reaction characteristics. We also have tried to shed light on the utility and environmental friendliness of molecular oxygen and activated carbon in the oxidation[4] and extend the reaction examples. The reaction yields and reaction time (1 h in most cases) were dramatically improved by use of dried activated carbon (200 ℃ for 10 h) and molecular oxygen continuously bubbling into the solvent. Thus, a mixture of 1,2-phenylenediamine (0.5 g, 4.62 mmol), aromatic aldehyde (4.62 mmol), and activated carbon (Darco KB, 0.25 g, 50 weight%) was heated at 110-115 ℃ for 1 h in xylenes (40 mL) with stirring under bubbling of molecular oxygen into xylenes. After filtration, the usual workup of xylenes evaporation and SiO_2-purification gave the corresponding benzimidazoles in the yields shown in Table 1. As can be seen from Table 1, we obtained the desired benzimidazoles in good to excellent yields. After the filtered activated carbon was dried, it was reused several times to afford almost the same results as those in Table 1. It is of interest to note that without activated carbon almost no reaction proceeded and the fact indicated us the important role of activated carbon in the present reaction.

Table 1



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

Entry	RCHO	Product	Yield (%)	Entry	RCHO	Product	Yield (%)
1		3a	90	6		3f[8]	82
2		3b	86	7		3g[5]	83
3		3c[5]	91	8		3h[7]	85
4		3d[6]	87	9		3i[9]	92
5		3e[7]	84	10		3j[7]	93

a) A.C. = activated carbon (Darco KB)

While in the reaction of 1,2-phenylenediamine with 4-(dimethylamino)benzaldehyde in the presence of certain oxidant like oxone the side reaction occurred to afford 2*H*-benzimidazole,[2] the present reaction gave the corresponding benzimidazole in good yield (Entry 8). In summary, we revealed some features of the present reaction; 1) the reaction comprises very simple procedures and simple workup gave the corresponding benzimidazoles in good yields, 2) the reaction would be compatible with aromatic aldehydes having redox-sensitive substituents, 3) the reaction is the environmental friendliness due to the use of reusable activated carbon and molecular oxygen. It would also be interesting to explore the reaction of 1,2-phenylenediamine derivatives with a variety of aldehydes (aliphatic, aromatic and heteroaromatic) bearing electron-donating and electron-withdrawing substituents. The present reaction should be equally applicable to the preparation of benzoxazole and related classes of fused heterocycles. From these standpoints, our investigation is currently under way.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded on the following spectrometers: ^{1}H nmr spectra, JEOL GX-400 (400 MHz) and JEOL A-500 (500 MHz); ^{13}C nmr spectra, JEOL GX-400 (100 MHz) and JEOL A-500 (125MHz); mass spectra, JEOL JMS-DX300 for EI-ms and JMS-HX110 for FAB-ms. The HH-COSY, CH-COSY, and DEPT experiments were also used for the assignments of the structures. The chemical shifts are given on the δ scale. Elemental analyses were performed on a Heraeus CHN-O-RAPID instrument. Medium pressure liquid chromatography (mplc) was carried out with a Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40 μm, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).

General Procedure for reaction of 1,2-phenylenediamine with aromatic aldehyde in the presence of activated carbon and molecular oxygen

A mixture of 1,2-phenylenediamine (0.5 g, 4.62 mmol), aromatic aldehyde (4.62 mmol), and activated carbon (Darco KB, 0.25 g, 50 weight%) was heated at 110-115 ℃ for 1 h in xylenes (40 mL) with stirring under bubbling of molecular oxygen into xylenes. The resulting solution was filtered and the filtrate was furthermore filtered with Celite, washing with MeOH. After removal of the solvent, the residue was worked up in the manner as shown below.

2-(3,4,5-Trimethoxyphenyl)-1*H*-benzimidazole

This compound was recrystallized from AcOEt to give colorless cottony crystals, mp 267 ℃. ^{1}H NMR(DMSO-d_6) δ (ppm): 3.75 (3H, s, Me), 3.91(6H, s, Me×2), 7.20 (2H, s, Ar-H), 7.52 (3H, s, Ar-H), 7.53 (1H, Ar-H), 12.81(1H, s, NH). ^{13}C NMR(DMSO-d_6) δ (ppm): 20.3 (q, Me), 56.1 (q, Me×2), 60.1 (q, Me), 103.9 (d, Ar), 111.1 (d, Ar), 118.6 (d, Ar), 121.6 (d, Ar), 122.4 (d, Ar), 125.4 (s, Ar), 139.0 (s, Ar), 151.2 (s, Ar), 153.2 (s, Ar). EI-ms m/z(%): 284 (M^+, 100), 269(37), 241(8), 211(12), 142(10). *Anal*. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.70; N, 9.88.

2-(2,4-Dichlorophenyl)-1*H*-benzimidazole

This compound was recrystallized from benzene to give colorless scales, mp 232 ℃. ^{1}H NMR(DMSO-d_6) δ (ppm): 7.25 (2H, br s, Ar-H), 7.58-7.60(1H, br s, Ar-H), 7.95 (1H, d, J = 8.5Hz, Ar-H), 12.75(1H, s, NH). ^{13}C NMR(DMSO-d_6) δ (ppm): 111.8 (d, Ar), 119.1 (d, Ar), 121.8 (d, Ar), 122.9 (d, Ar), 127.7 (d, Ar), 128.8 (s, Ar), 129.8 (d, Ar), 132.6 (s, Ar), 133.2 (d, Ar), 134.6 (s, Ar), 135.0 (s, Ar), 143.1 (s, Ar), 148.0 (s, Ar). EI-ms m/z(%): 266(11), 264(65), 262(M^+, 100), 192(9), 90(8). *Anal*. Calcd for $C_{13}H_8N_2Cl_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.35; H, 3.15; N, 10.63.

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