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Cerium (IV) ammonium nitrate (CAN) promoted reaction: A selective synthesis of 2-arylbenzimidazoles *via* reaction of *o*-phenylenediamine and arylidene malononitriles at ambient temperature

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Dedicated to the memory of Prof. Dr. M. H. Elnagdi

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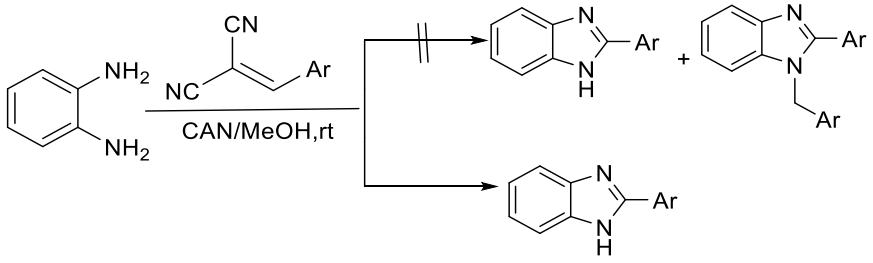
Abstract

Cerium (IV) ammonium nitrate was utilized as an efficient catalyst for the selective green synthesis of 2-arylbenzimidazole derivatives *via* one-pot reaction of *o*-phenylenediamine and arylidene malononitriles in methanol at ambient temperature. The process proved to be selective, simple, atom economical with excellent yields. The Ecoscale score of the reaction was calculated and reveals a high record.



Keywords: Selective synthesis, 2-arylbenzimidazole, ceric ammonium nitrate (CAN), room temperature, excellent yields, high EcoScale

Introduction

Benzimidazoles possess significant position as biodynamic naturally occurring active compounds. [1-5] They are widely found in pharmaceuticals, agrochemicals as well as synthetic drugs. [6-7] Many benzimidazole Scaffolds are utilized for their anticancer, [8-9] antimicrobial, [10-12] anti-inflammatory[13] antiviral, [14-15]antifungal,[16] analgesic [18-19] as well as antibacterial [20] activities. This Scaffold has also been an important ligand for several receptors as tubulin polymerase, [21] DNA topoisomerase (I) [22] estrogen [23], and as efficient alternative of toxic and air-moisture-sensitive phosphine-based ligands in Heck-Mizoroki and Suzuki cross coupling reactions.[24] Examples of marketed drugs incorporation benzimidazole moiety are illustrated in (Figure 1).

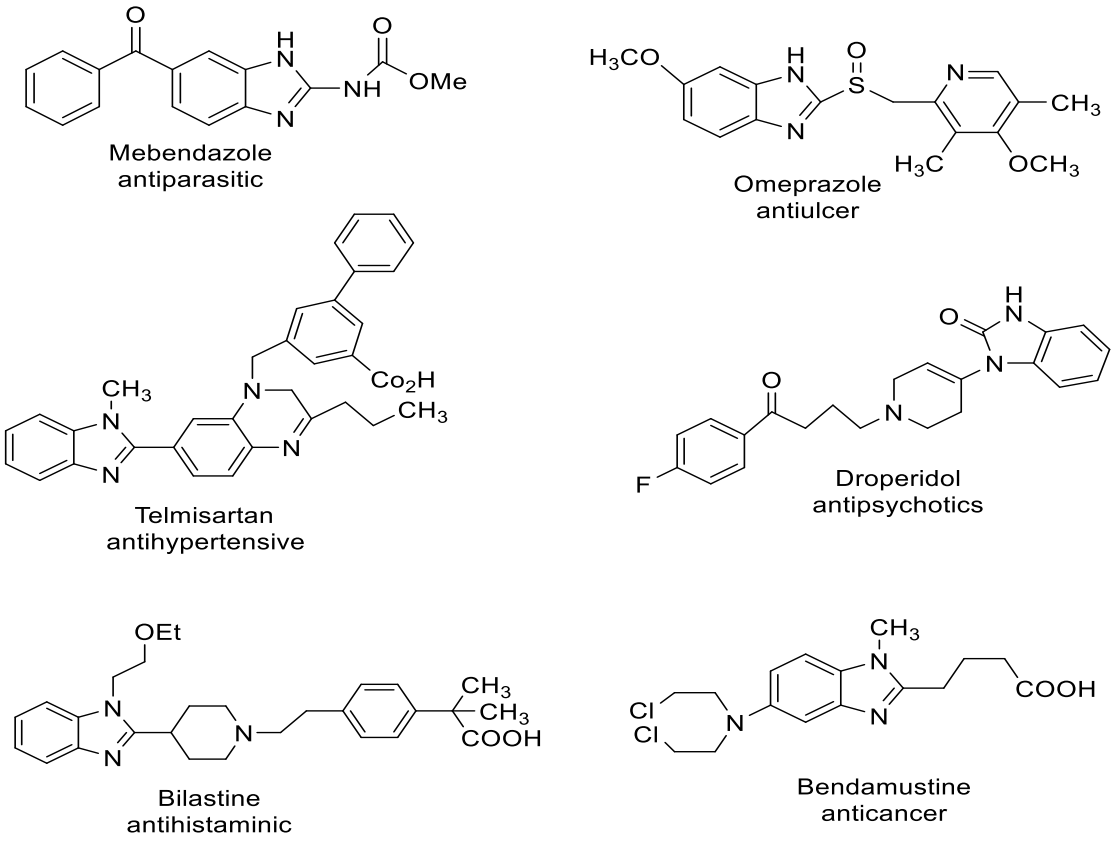


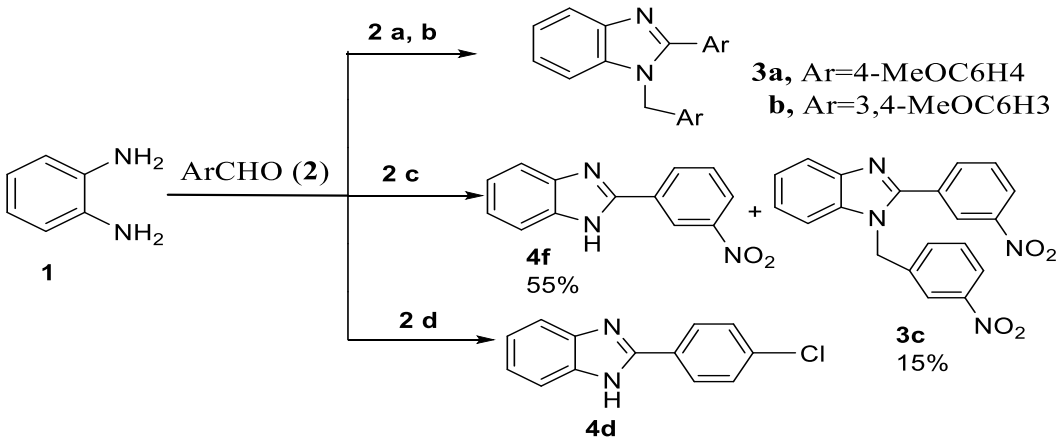
Figure 1. Examples of marketed drugs incorporating benzimidazole moiety.

Several synthetic approaches for the synthesis of benzimidazoles have been relied on oxidative cyclization reaction of *o*-phenylenediamine with aldehydes, carboxylic acids, lactones and esters in Strong acidic medium in particular hydrochloric acid as well as sulphuric, polyphosphoric and acetic acids.[24] To date, metal-catalysed synthesis of benzimidazoles has considerable interest as an efficient synthetic protocol. However, they involve harsh reaction conditions including the use of complex ligands and poor substrate with longer reaction times. [25-36] An intriguing approach for the synthesis of 2-arylbenzimidazoles have been recently developed by Chopra, Kumer and Bhalla through a photocatalytic sequential amination, azidation and annulation reaction of aniline with methyl arenes catalysed by recyclable PANI@Au:CuoNCS promoted by visible light.[37] Recently, two reports dealing with the synthesis of diverse 2-arylbenzimidazoles have been previously reported. Su et al in 2009 [38] developed high yield synthesis via reaction between

o-phenylenediamine and arylmethylene malononitriles absorbed on silica gel at 90 °C. While the second protocol developed by Kapoor [39] and co-authors relied on the reaction of o-phenylenediamine with ethyl α-cyanocinnamate in oil bath at 100°C. Although these methods have their advantages, but they suffer from drawbacks as prolonged heating, low yields, harsh reaction conditions, use of expensive and toxic catalysts as well as tedious conducting the reaction or working-up the product isolation.

Ceric ammonium nitrate (CAN) has been emerged as green, atom economical and easily available catalyst for performing organic transformations. It possesses several merits as eco-friendly, coast effective and profound activity properties. (CAN) with its wide application in organic synthesis can belong to three categories, a) one-electron oxidant via generation of radical and radical cation species through the reduction of its oxidation state from Ce (IV) to Ce (III) which is the most commonly utilized proposed mechanism; b) the second is the generation of protons as a Brønsted acid via hydrolysis of nitrate anion; c) as a Lewis acid catalyst via 3rd empty orbitals of cerium. In addition, very small amount needed to complete efficiently reactions with lower coasts, environmentally friendly nature, nontoxicity, high reactivity and ease of handling.[40]

We have previously reported the reaction of *o*-phenylenediamine with aromatic aldehydes in methanol catalysed with 10 mol % CAN at ambient temperature. [41] The results obtained revealed that aromatic aldehydes bearing electron donating substituents afforded solely the 2-aryl-1-arylmethyl benzimidazole derivatives **3a,b.** Aryl aldehydes with 3-nitro electron attraction substituent yielded a mixture of 2-(3-nitrophenyl)-benzimidazole 4f and the 1-arylmethyl derivative 3c in 55: 15% yields. However, 4-chlorosubstituted aldehyde **2d** afforded mainly the mono-2-arylsubstituted benzimidazole **4a**. (Scheme 1)

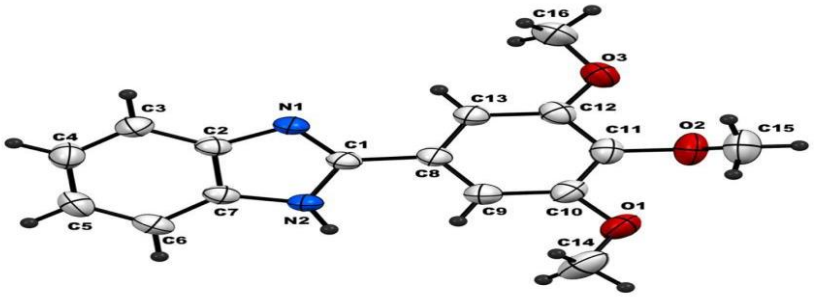


Scheme 1

In the context of our interest in performing efficient and green methodologies [42-46] for the synthesis of biologically relevant heterocycles, we reported here in an efficient selective synthesis 2-arylbenzimidazole via reaction of *o*-phenylenediamine (**1)** with arylidene malononitriles **5a-j** as aldehyde equivalents promoted by (CAN) in methanol at ambient temperature.

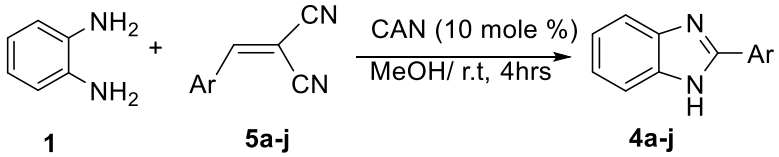
Results and Discussion

In the beginning we examined the feasibility of *o*-phenylenediamine **1** (0.01 mol) and 4-chlorobenzylidene malononitrile (**5a**) (0.01 mol) in acetonitrile (10 ml) using CAN (10 mol %) at ambient temperature which afforded a product of molecular formula $C_{13}H_9ClN_2$ (MS= 228.93) in 70% yield. ^{1}H NMR revealed broad singlet at δ=7.22 ppm and two multiplets at δ=7.61 – 7.67; 8.18 – 8.21 for aromatic protons. In additions, it showed broad singlet at δ=13.00 ppm for benzimidazole (NH). This established the formation of the corresponding 2-arylbenzimidazole derivative **4a.** ^{13}CNMR measurements further support the proposed structure. Moreover, the structure of **4e** was unambiguously confirmed by single-crystal diffraction [47]



Prompted by this result in hand be we tried different reaction conditions. First, we examined several solvents as $CHCl_3$, H_2O, dioxane and MeOH. Methanol afforded the highest yield (95%). The Solvent free conditions were found to yield a lower yield (40%) compared to that conducted in methanol. Different molar ratios of CAN (2, 5, 15, 20 mol %) were tested and results demonstrated that 10 mol % of CAN is the optimum to promote the highest yield of **4a**. Moreover, catalyst-free conditions afforded the starting materials unreacted even after stirring for 24 hours. This reflects the crucial role of CAN in the reaction course.

To evaluate the generality of this protocol for producing a diverse 2-arylbenzimidazoles **4a-g** several arylidene malononitriles were investigated (Table 1) under the same experimental conditions. The results obtained revealed that the reaction proceeds smoothly with high yields with arylidene-malononitriles bearing either electron withdrawing or electron donating substituents. The same applies when aryl ring was replaced by furyl function. As generally expected, the reactions proceed at ambient temperature in four hours. (Scheme 2)



Scheme 2

Table 1. Comparison of melting points of compounds prepared with literature values

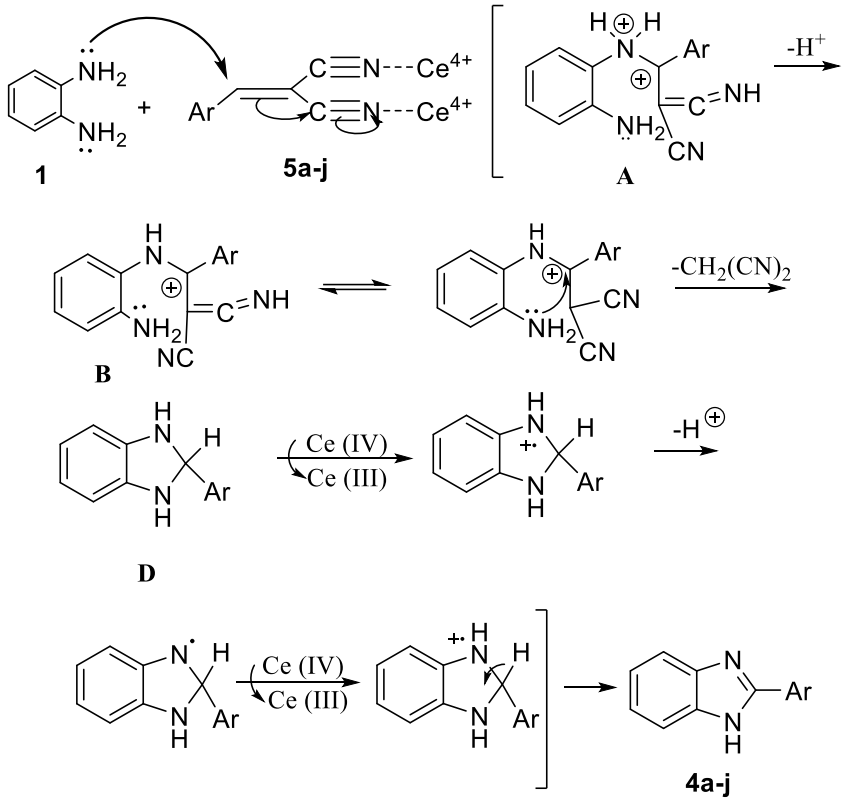
Compd.	Ar	mp ^{o}C	Lit. mp
4a	4-ClC_6H_4	291-293	292-294 [38]
4b	4-$OCH_3C_6H_4$	222-224	223-226 [49]
4c	2-$OCH_3C_6H_4$	218-220	217-219 [50]
4d	3-$OCH_3C_6H_4$	211-212	210-214 [38]
4e	3, 4, 5- $OCH_3C_6H_2$		
4f	3-$NO_2C_6H_4$	202-204	202-203 [38]
4g	4-$NO_2C_6H_4$	301-303	299-301 [38]
4h	3-ClC_6H_4		
4i	4-OHC_6H_4	208-210	
4J	3-furanyl	333-335	330-332 [38]

We estimate the greens of the reaction through calculatin the EcoScale [48] of compound **4c** with the highest yield products of other key protocols. EcoScale is a novel theoretical tool based on several issues involving yield, cost, safety, temperature for conducting the reaction, ease of work up and purification, technical steps. It is estimated by range of penalty points subtracted from total of 100. We found our procedure have the highest EcoScales among other protocols (Table 2).

Table 2. Comparison of EcoScale of literature reported synthesis of 2-aryl-benzimidazole derivatives

Product	Solvent	Catalyst	Temp. (^{o}C)	Time (hrs)	Yield	EcoScale
4b	Neat	Silica-Supported	90	0.5	95	85.5 [39]
4a	Neat	-	100	1	75	74.5 [40]
4c	MeOH	CAN	Ambient temp	4	95	95.5

A plausible mechanism to account for the formation of the reaction products was proposed in (Scheme 2). Ceric ammonium nitrate as a Lewis acid facilitate the nucleophilic addition of *o*-phenylenediamine (**1**) to the activated double bond system of arylidene-malononitrile yielding intermediate (**A**) followed by nucleophilic attach of nitrogen lone-pair to the positively charged methine carbon and subsequent malononitrile loss forming intermediate (**D**). Aromatization of intermediate (**D**) by the action of CAN as a one-electron oxidant afforded the final isolable product 4 (Scheme 3).



Scheme 3

Conclusions

We could develop a selective and efficient synthesis of 2-arylbenzimidazoleles via reaction of *o*-phenylenediamine with arylidene-malononitriles utilizing for the first time. CAN as a green catalyst at ambient temperature. Such selectivity could be rationalized for by the better stability of arylidene-malononitriles relative to some aldehydes. The process proved to be simple, atom economical and environmentally friendly nature.

Experimental Section

General. Melting points were measured on a Gallenkamp melting point apparatus and were uncorrected. The progress of the reaction was followed by thin layer chromatography on pre-coated Merck Silica gel ($60F_{254}$) aluminum sheets. ^{1}H NMR and ^{13}C NMR were recorded on a Balker DPX at (400) MHz and (100) MHz for ^{13}C spectra Mass spectra were determined on a VG Autospec QMS 30 spectrometer at 70 ev. Microanalytical data were obtained from the microanalytical data unit.

General procedure for the synthesis of 2-arylbenzimidazoles (3a). To a solution of *o*-phenylenediamine **(1)** (0.01 Mol.) and the appropriate arylidene-malononitriles **(2)** (0.01 Mol.) in methanol (10 ml) was added 10 mol % of Cerium ammonium nitrate (CAN). The reaction mixture was stirred at ambient temperature for 4 hours.

The solid product formed was collected by filtration and crystalized from ethanol to afford analytically pure samples of **4a-j**.

2-(4-Chlorophenyl)-1*H*-benzimidazole (4a). White solid, yield 95% ^{1}H NMR (400 MHz, DMSO-d_6), δ 7.22 (br.S. 2H, Ar-H), 7.61 – 7.67 (m, 4H, Ar-H), 8.18-8.21 (m, 2H, Ar-H), 13.00 (S, 1H, NH); ^{13}C NMR (100 MHz, DMSO- d_6): δ 111.40, 118.94, 121.82, 122.75, 128.12, 129.04, 134.47, 135.01, 143.72, 150.13. Anal. Calcd. For $C_{13}H_9ClN_2$ (228.68): C, 68.28; H, 3.97; N, 12.25. Found C, 68.33; H, 3.89; N, 12.35; MS(EI); *m/z* 228.39 (M^+).

2-(4-Methoxyphenyl)-1*H*-benzimidazole (4b). Red Solid, yield 92%. ^{1}H NMR (400 MHz, DMSO- d_6): δ 3.84 (S, 3H, OCH3), 7.12 (d, 2H, *J* 8.8 Hz, 2H, Ar-H); 7.18-7.20 (dd, 2H, J_1, J_2 3.2 Hz, Ar-H). 7.57, 7.59 (dd, 2H, J_1 3.2 Hz, J_2 4.8 Hz, Ar-H), 8.14 (d, 2H, *J* 9.2 Hz, Ar-H, 13C NMR (100 MHz, DMSO- d_6): δ 55.31, 114.02, 114.38, 114.72, 121.90, 122.42, 128.08, 130.55, 139.15, 151.28, 160.70. Anal. Calcd. For $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49; Found: C, 74.88; H, 5.36; N, 12.52%. MS (EI); *m/z* 224.04 (M^+).

2-(2-Methoxyphenyl)-1*H*-benzimidazole (4c). Brown Solid, yield 90%. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 3.81 (S, 3H, OCH3), 7.11-7.15 (m, 1H, Ar-H); 7.20, 7.22 (dd, 2H, J_1 3.2; J_2 3.2 Hz). 7.24 (d, 1H, *J* 8 Hz, Ar-H), 7.47-7.51 (m, 1H, Ar-H), 7.63, 7.65 (dd, 2H, J_1 J_2 3.2 Hz, Ar-H), 8.32, 8.34 (dd, 1H, J_1 1.6 Hz, J_2 2 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 55.75, 112.10, 115.14, 117.89, 120.86, 121.89, 129.73, 131.35, 138.49, 148.85, 156.78. Anal. Calcd. For $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49; Found: C, 75.01; H, 5.38; N, 12.52%. MS (EI); *m/z* 224.08 (M^+).

2-(3-Methoxyphenyl)-1*H*-benzimidazole (4d). White Solid, yield 91%. ^{1}H NMR (400 MHz, DMSO- d_6): δ =3.87 (S, 3H, OCH_3), 7.05-7.08 (m, 1H, Ar-H), 7.21, 7.23 (dd, 2H, J_1 J_2 3.2Hz, Ar-H), 7.46 (b, 1H, *J* 8.4 Hz, Ar-H); 7.60, 7.62 (dd, 2H, J_1 J_2 3.2Hz, Ar-H), 7.76-7.78 (m, 2H, Ar-H), 13.22 (br. S. 1H, NH). ^{13}C NMR: (100 MHz, DMSO- d_6): δ= 55.27, 111.39, 115.08, 115.89, 118.74, 122.18, 130.09, 131.38, 151.05, 159.63. Anal. Calcd. For $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.85; H, 5.22; N, 12.55%. MS(EI); *m/z* 224.06 (M^+).

2-(3,4,5-Trimethoxyphenyl)-1*H*-benzimidazole (4e). Yellow solid, yield 94%. ^{1}H NMR (400 MHz, DMSO- d_6): δ =3.74 (S, 3H, OCH_3), 3.91 (S, 6H, two OCH_3 functions), 7.19-7.23 (m, 2H, Ar-H), 7.54 (d, 2H, J= 4.8 Hz, Ar-H), 7.60, 7.62 (dd, 2H, J_1 J_2 3.2 Hz, Ar-H), 12.86 (br.s. 1H, NH). ^{13}C NMR: (100 MHz, DMSO- d_6): δ 55.85, 56.01, 59.98, 103.81, 106.70, 114.15, 122.03, 125.46, 130.25, 137.05, 138.89, 151.21, 152.83, 153.22. Anal. Calcd. For $C_{16}H_{16}N_2O_3$ (284.32): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.66; H, 5.71, N, 9.87%. MS(EI); *m/z* 284.22 (M^+).

2-(3- Nitrophenyl)-1*H*-benzimidazole (4f). Yellow solid, yield 92%. ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.25, 7.26 (dd, 2H, J_1 J_2 3.2 Hz, Ar-H), 7.72 (d, 1H, *J* 8 Hz, Ar-H), 8.20 – 8.23 (m, 1H, Ar-H), 8.60-8.62 (m, 1H, Ar-H), 8.31-8.34 (m, 2H, Ar-H), 9.01 (b, 1H, *J* 2H, Ar-H); 13.20 (br.S.1H, NH). Anal. Calcd. For $C_{13}H_9N_3O_2$ (239.23): C, 65.27; H, 3.79; N, 17.56. Found: C, 65.21; H, 3.82; N, 17.55%. MS(EI); *m/z* 239.23 (M^+).

2-(4- Nitrophenyl)-1*H*-benzimidazole (4g). Yellow solid, yield 93%. ^{13}C NMR (100 MHz, DMSO- d_6): δ 113.77, 122.94, 128.22, 130.20, 136.28, 136.93, 147.79. Anal.Calcd. for $C_{13}H_9N_3O_2$ (239.23): C, 65.27; H, 3.79; N, 17.56. Found: C, 65.33; H, 3.72; N, 17.55%. MS(EI); *m/z* 239.25 (M^+).

2-(3- Chlorophenyl)-1*H*-benzimidazole (4h). Yellow solid, yield 91%. ^{13}C NMR (100 MHz, DMSO- d_6): δ= 122.42, 124.98, 126.00, 129.50, 130.89, 132.17, 133.75, 149.70. Anal.Calcd. for $C_{13}H_9ClN_2$ (228.05): C, 68.28; H, 3.97; Cl, 15.50; N, 12.25. Found: C, 68.32; H, 3.92; N, 12.31%. MS(EI); *m/z* 227.99 (M^+).

2-(4- Hydroxyphenyl)-1*H*-benzimidazole (4i). Brown crystals yield 89%. ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.00-7.06 (m, 2H, Ar-H), 7.26-7.30 (m, 2H, Ar-H), 7.36-7.43 (m, 1H, Ar-H), 7.66, 7.67 (dd, 2H, J_1 J_2 3.6 Hz, Ar-H), 7.86 (br.s.1H, OH), 8.06, 8.08 (dd, 1H, J_1 1.2, J_2 1.6 Hz, Ar-H), 13.20 (br.s.1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6): δ 112.58, 117.18, 119.10, 122.82, 126.20, 131.71, 146.88, 151.69, 158.02, 172.62. Anal.Calcd. for $C_{13}H_{10}N_2O$ (210.08): C, 74.27; H, 4.79; N, 13.33. Found, C, 74.35; H, 4.82; N, 13.21%. MS (EI); *m/z* 210.13 (M^+).

2-(3- furanyl)-1*H*-benzimidazole (4j). Yellow solid, yield 88%. ^{13}C NMR (100 MHz, DMSO- d_6): δ= 122.15, 126.66, 128.24, 128.72, 133.66, 146.99. Anal.Calcd. for $C_{11}H_8N_2S$ (200.26): C, 65.98; H, 4.03; N, 13.99; S, 16.01. Found: C, 65.95; H, 4.16; N, 14.05; S, 16.14%. MS(EI); *m/z* 200.13 (M^+).

Supplementary Material

Copies of ^{1}H NMR, ^{13}C NMR and MS spectra of synthetized compounds are available on the supplementary material file associated with this paper.

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