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Synthesis of 2-Substituted Benzimidazoles and Bis-benzimidazoles by Microwave in the Presence of Alumina-Methanesulfonic Acid

K. Niknam* and A. Fatehi-Raviz
Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran

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A microwave-assisted method for the synthesis of 2-substituted benzimidazoles in the presence of alumina-methanesulfonic acid (AMA) is reported. In addition, by this method some new bis-benzimidazoles from the direct reaction of phenylenediamine and dicarboxylic acid under microwave irradiation in good to excellent yields are described.

Keywords: Benzimidazoles, Bis-benzimidazoles, 1,2-Phenylenediamine, Carboxylic acids, Alumina-methanesulfonic acid, Microwave irradiation

INTRODUCTION

Structures containing benzimidazole, well-known to have a wide range of biological properties, have commercial applications in various realms of therapy, including anti-ulcerative, anti-hypertensive, antiviral, antifungal, anti-tumor and antihistaminic agents, and antihelminthic agents in veterinary medicine [1]. Furthermore, these heterocycles are considered to be privileged structures by medicinal chemists. To gain accessible chemistry space not attainable by current methods, the development of new synthetic methods will be very important to the chemistry community. Hence, investigation into rapid means to synthesize benzimidazoles would be highly beneficial.

The most commonly-used synthetic approaches typically entail the condensation of an arylenediamine with a carbonyl equivalent [2]. Likewise, esters, lactones and anhydrides could produce benzimidazoles through the cyclization of amide. However, this might have a limited scope, since the necessary reaction conditions are harsh and result in a meager assortment of final products. For example, the reaction of arylenediamines with aliphatic esters and lactones, which uses strong mineral acids at high temperatures, necessitates conditions that would not allow for a wide range of functional groups and attractive substrates.

In addition, there have been numerous reports about synthesis via the reductive cyclization of *o*-nitroanilines with aldehydes [3] and cyclization of *o*-nitroaniline derivatives with aryl isothiocyanates catalyzed by bismuth chloride [4] and mercury chloride [5], and Baker's yeast reduction of 2,4-dinitroacylanlines [6]. Ionic liquids [7] have been shown to promote the synthesis of 2-aryl benzimidazoles, benzoxazoles and benzothiozoles by the reaction of phenylenediamine and various acid chlorides. Commercially-available PS-Ph_3 resin combined with microwave heating delivers a variety benzoxazoles and benzimidazoles from carboxylic acids [8].

Iodine and potassium iodide in water have produced corresponding benzimidazoles by the reaction of aldehydes and phenylenediamine [9], and by the reaction of phenylenediamine and aldehydes in the presence of silica sulfuric acid to produce selective 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles [10].

*Corresponding author. E-mail: niknam@pgu.ac.ir

We have previously reported that a mixture of AMA is an effective reagent for the conversion of alcohols into corresponding amides [11], Fries-rearrangement [12], Beckmann rearrangement [13], hydration of nitriles into amides [14], monoesterification of diols [15], N-nitrosation of secondary amines [16], and aromatization of 1,4-dihydropyridines [17]. In continuation of our work on the applications of AMA as a catalyst in organic reactions, herein we report the synthesis of benzimidazoles by the reaction of *ortho*-phenylenediamine and carboxylic acids in the presence of AMA under microwave irradiation.

EXPERIMENTAL

Chemicals and Apparatus

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. IR spectra were acquired on a Shimadzu infra red spectrometer, model IR-435. The ^{1}H NMR spectra were obtained on a JEOL NMR spectrometer, model FX 90Q, and Bruker Avance (DRX 500 MHz). Melting points were recorded on a SMP1 melting point apparatus (Stuart Scientific, UK) in open capillary tubes and are uncorrected. The progress of the reaction was followed by TLC using silica gel SILG/UV 254 plates. A MW domestic oven, 900 W, with a frequency of 2450 MHz, Multiwave, from LG, Korea was used.

General Procedure for the Synthesis of Benzimidazoles

A mixture of 1,2-phenylenediamine (2.5 mmol, 0.27 g), carboxylic acid (3.75 mmol), alumina (0.33 g) and methanesulfonic acid (6 mmol, 0.39 g) were finely ground in a screw-capped teflon vessel. Microwave irradiation at 20% power was applied for times specified. The progress of the reaction was followed by TLC. After completion of the reaction, water was added to the reaction mixture, filtered, and washed with warm water to separate the alumina. The resulting aqueous extracts were combined neutralized with sodium bicarbonate. The precipitates were isolated by filtration, washed with water (2 × 15 ml) and air dried to afford the desired product with satisfactory purity. The precipitated products with lower purity were further purified by column chromatography on silica gel. The benzimidazole products were characterized by comparison of their spectral (IR, ^{1}H NMR), TLC and physical data with the authentic samples [3,6,7,18].

General Procedure for the Synthesis of Bis-benzimidazoles

A mixture of 1,2-phenylenediamine (5 mmol, 0.54 g), carboxylic acid (3.75 mmol), alumina (0.5 g) and methanesulfonic acid (12 mmol, 0.78 g) were finely ground in a screw-capped teflon vessel. Microwave irradiation (MW domestic multiwave oven, 900 W, with a frequency 2450 MHz, LG, Korea) at 20% power was applied for times specified. The progress of the reaction was followed by TLC. After completion of the reaction, water was added to the reaction mixture, filtered, and washed with warm water to separate the alumina. The combined aqueous extracts were neutralized by sodium bicarbonate. The precipitates were then filtered, washed with water (2 × 15 ml) and air dried to afford the desired product in satisfactory purity. The precipitated products with lower purity were further purified by recrystallization from ethanol.

Selected Spectral Data

2-(2-pyridyl)benzimidazole (3l). m.p.: 217-219 ºC, (Lit. [19]: 218-220 ºC; IR (KBr): 3450, 3050, 1590, 1439, 1310, 1277, 740 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 7.18-7.21 (m, 2H), 7.50 (t, 1H, J = 6.50 Hz), 7.60-7.61 (m, 2H), 7.98 (t, 1H, J = 7.70 Hz), 8.31 (d, 1H, J = 7.70 Hz), 8.71 (d, 1H, J = 4.5 Hz), 13.04 (br, 1H). ^{13}C NMR (DMSO-d$_6$, 125 MHz), δ: 121.32, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28, 150.66; MS (m/z %): 196 [M$^+$+1] (31.15), 195 [M$^+$] (base peak), 167 (33.23), 105 (12.48), 90 (9.93), 78 (16.93).

Bis((1H-benzo[d]imidazol-2yl)methyl)sulfane (5b). m.p.: 210-212 ºC (dec.), (Lit. [18]: 212 ºC dec.); IR (KBr): 3388, 3050, 1590, 1439, 1273, 742 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 4.05 (s, 4H), 7.15-7.17 (m, 4H), 7.50-7.52 (m, 4H), 12.45 (br, 2H). ^{13}C NMR (DMSO-d$_6$, 125 MHz), δ: 28.76, 111.91, 118.67, 121.77, 151.72; MS (m/z %): 295 [M$^+$+1] (27.66), 294 [M$^+$] (85.56), 163 (12.03), 132 (base peak), 104 (90.82), 77 (9.39).

2-(((1H-benzo[d]imidazol-2-yl)methoxy)methyl)-1H-benzo[d]imidazole (5c). m.p.: 296-298 ºC (dec.); IR (KBr): 3408, 3050, 1592, 1439, 1270, 746 cm^{-1}. ^{1}H NMR (DMSO-d$_6$,

500 MHz), δ: 4.86 (s, 4H), 7.10-7.28 (m, 4H), 7.51-7.53 (m, 4H), 12.51 (br, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 66.13, 112.05, 118.78, 121.89, 151.05; MS (m/z %): 279 [M^++1] (0.68), 278 [M^+] (0.74), 248 (base peak), 194 (6.66), 167 (2.91), 131 (39.47), 104 (11.44), 91 (15.27), 77 (15.61).

2-(6(1H-benzo[d]imidazol-2-yl)pyridine-2-yl)-1H-benzo[d] imidazole (5d). m.p.: > 250 ºC, (Lit. [18]: > 250 ºC); IR (KBr): 3408, 3050, 1592, 1439, 1270, 743 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 7.26-7.28 (m, 4H), 7.70-7.72 (m, 4H), 8.11 (d, 2H, J = 7.50 Hz), 8.31 (t, 1H, J = 7.50 Hz), 12.48 (br, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 121.45, 123.00, 124.81, 139.14, 147.74, 150.00, 150.50; MS (m/z %): 297 [M^+] (0.63), 283 (8.78), 239 (base peak), 221 (61.35), 195 (74.25), 194 (99.12), 167 (37.52), 105 (14.15), 90 (19.32), 77 (3.51).

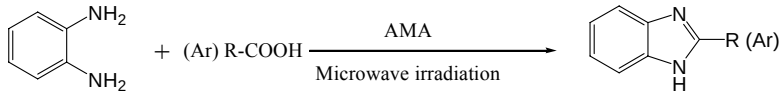
2-((2-((1H-benzo[d]imidazol-2yl)methoxy)phenoxy) methyl)-1H-benzo[d]imidazole (5e). m.p.: 223-224 ºC; IR (KBr): 3408, 3050, 1592, 1439, 1270, 743 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 5.29 (s, 2H), 5.34 (s, 2H), 6.88-6.92 (m, 4H), 7.15-7.18 (m, 6H), 7.54-7.56 (m, 4H), 12.48 (br, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 65.10, 113.78, 115.00, 115.44, 121.47, 122.08, 147.62, 147.98, 150.22; MS (m/z %): 332 [M+] (0.18), 248 (55.38), 167 (7.36), 149 (17.79), 131(19.69), 104 (7.67), 91 (24.0), 69 (79.38), 43 (base peak).

RESULTS AND DISCUSSION

Recently, medicinal chemists have taken great interest in the combinatorial methods for the design and synthesis of pharmacologically-relevant heterocyclic molecules [20]. Inexpensive and readily-available domestic microwave ovens transform electromagnetic energy into heat, thus the absorption and transmission of the energy varies greatly from that of conventional heating. Solid-phase approaches for benzimidazole synthesis have been published [21], however the cyclization of benzimidazole catalyzed by alumina-methanesulfonic acid (AMA) under microwave irradiation has not been reported.

In the present study, the appropriate carboxylic acids were reacted with 1,2-phenylenediamine in the presence of AMA under microwave irradiation to give the corresponding benzimidazoles in good to excellent yields (Scheme 1).

In a preliminary study, we examined the reaction of benzoic acid and 1,2-phenylenediamine in the presence of under microwave irradiation and optimized the reaction conditions. The best microwave irradiation power level was 20%. With the first successful result in hand, synthesis of other 2-substituted benzimidazole derivatives was carried out under similar reaction conditions (Table 1). As shown in Table



2$_{a-l}$ **3$_{a-l}$**

Scheme 1

Table 1. The Reaction of *o*-Phenylenediamine with Carboxylic Acids in the Presence of **AMA** under Microwave Irradiation

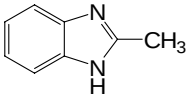
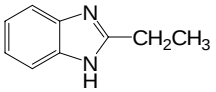
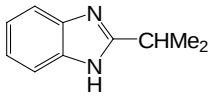
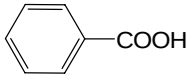
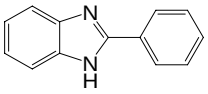
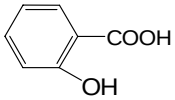
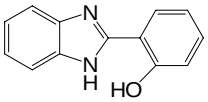
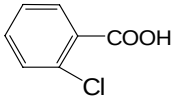
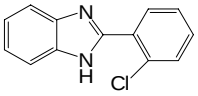
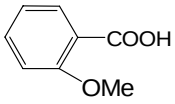
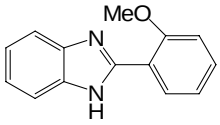
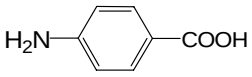
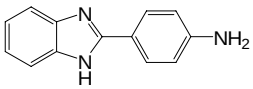
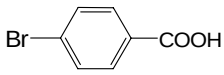
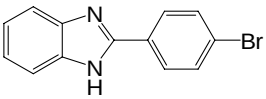
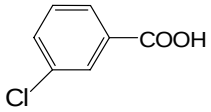
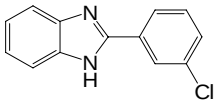
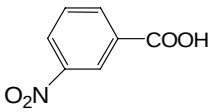
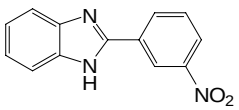
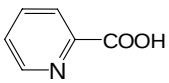
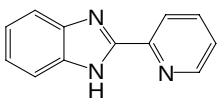
Entry	Carboxylic acid	Time (min)	Product	Yield (%)[a]
1	CH_3COOH **2a**	8	 **3a**	87
2	CH_3CH_2COOH **2b**	12	 **3b**	84

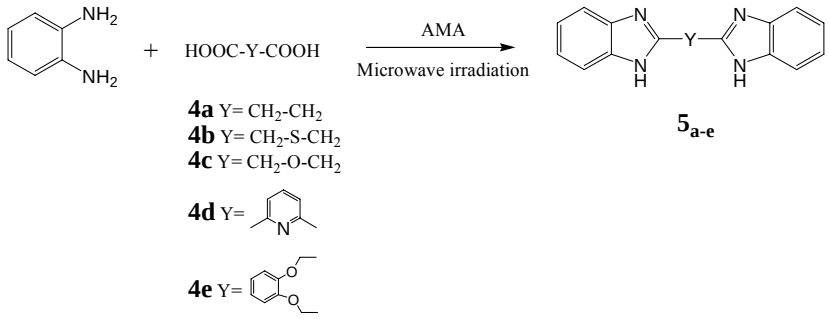
Table 1. Continued

3	$CH_3C(CH_3)$-COOH **2c**	4	 **3c**	85
4	 **2d**	10	 **3d**	96
5	 **2e**	18	 **3e**	81
6	 **2f**	4	 **3f**	83
7	 **2g**	4	 **3g**	78
8	 **2h**	4	 **3h**	83
9	 **2i**	4	 **3i**	80
10	 **2j**	4	 **3j**	79
11	 **2k**	7	 **3k**	77
12	 **2l**	4	 **3l**	78

[a]Isolated yields.

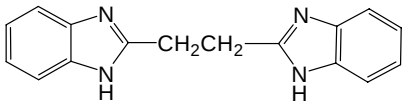
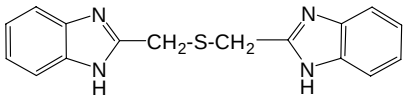
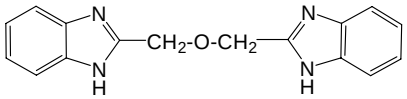
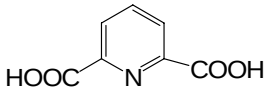
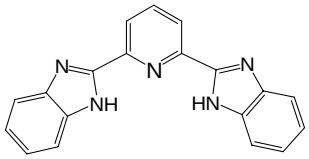
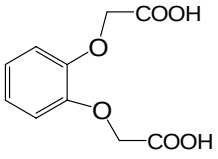
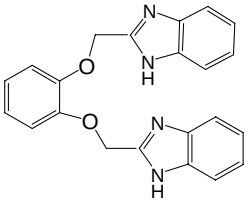
1, various types of aromatic and aliphatic carboxylic acids were reacted with 1,2-phenylenediamine at 20% power, and the corresponding benzimidazoles were obtained in good to excellent yields in short reaction times (2-18 min).

In addition, by this methodology bis-benzimidazoles were synthesized by the reaction of 1,2-phenylenediamine with various types of aliphatic and aromatic dicarboxylic acids. These results are summarized in Scheme 2 and Table 2.



Scheme 2

Table 2. The Reaction of *o*-Phenylenediamine with Dicarboxylic Acids in the Presence of **AMA** under Microwave Irradiation

Entry	Dicarboxylic acid	Time (min)	Product	Yield (%)[a]
1	$HOOCCH_2CH_2COOH$ **4a**	17	 **5a**	74
2	$HOOCCH_2$-S-CH_2COOH **4b**	16	 **5b**	85
3	$HOOCCH_2$-O-CH_2COOH **4c**	14	 **5c**	81
4	 **4d**	15	 **5d**	76
5	 **4e**	16	 **5e**	74

[a]Isolated yields.

In conclusion, we have shown another useful application of microwave irradiation in organic synthesis for the practical and efficient preparation of benzimidazoles and bis-benzimidazoles.

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