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An efficient synthesis of some new bisbenzimidazoles via microwave technique

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Abstract: 2,2'-[1,4 (1,3)-Phenylenedi(methylene)]bis-1*H*-benzimidazole derivatives were obtained from the reaction of 1,4- or (1,3)-bisiminoester hydrochloride and *o*-phenylenediamine derivatives under microwave irradiation. Ester and hydrazide derivatives were prepared from a free NH group. This practical method revealed good results for yield, reaction time, and quick isolation of products.

Key words: Bisbenzimidazole, bisiminoester hydrochloride, microwave synthesis, hydrazine hydrate

1. Introduction

Benzimidazoles are significant for many areas of chemistry.[1] They are contained in agrochemicals, dyestuffs, and high-temperature polymer products, and they have interesting biological and pharmaceutical activities.[2–6] Due to these facts, there has been significant attention paid to the synthesis of benzimidazole and bisbenzimidazole compounds in recent years. These kinds of heterocycles have also shown different pharmacological activities against gram-positive drug-resistant bacteria and some fungi, which are responsible for some infections in acute systems.[7]

The classical method for preparation of benzimidazole or bisbenzimidazole derivatives is via condensation of *o*-phenylenediamines with carboxylic acids under strong acid (polyphosphoric acid or mineral acid)/high temperature conditions or with corresponding aldehydes under oxidative conditions.[8–10] In recent years, various efficient synthetic methods have been developed. For example, trifluoromethylaryl ketones, orthoesters, and 1,3-dicarbonyl compounds have been used as an intermediate with 3,3'-diaminobenzidine for the synthesis of bisbenzimidazoles.[9,10] However, many of these methods involve challenges like expensive reagents, harsh reaction conditions, extended reaction times, occurrence of side products, and low yields. Therefore, there is a need for an efficient synthetic method that is short and economical for these types of compounds.

2. Experimental

2.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian Mercury spectrometer using TMS as an internal reference. The elemental analyses were determined on a Carlo Erba 1106 CHN analyzer; the measured percentages were in agreement ($\pm 0.2\%$) with the calculated ones. A monomode CEM-Discover Microwave apparatus was used in the standard configuration as delivered, including proprietary software. All

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experiments were carried out in microwave process vials (35 mL) with temperature controlled by an infrared detection temperature sensor. It was monitored by a computer and a constant temperature was maintained by discrete modulation of delivered microwave power. After completion of the reaction, the vial was cooled to 60 °C via air jet cooling. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54, 0.2 mm thickness).

2.2. Synthesis of compounds 3a–3c and 4a–4c

Compounds **1** or **2** (0.014 mol) and corresponding *o*-phenylenediamine derivative (0.02 mol) in methanol (10 mL) were taken in a closed vessel. The mixture was then irradiated in a microwave at 65 °C for 10 min (hold time) at 300 W maximum power. After the reaction was complete (monitored by TLC; ethyl acetate and hexane, 4:1), the mixture was left to cool to room temperature. The precipitate was filtrated, dried, and recrystallized from ethanol to yield the pure product.

2.2.1. 2,2'-[1,3-Phenylenedi(methylene)]bis-1*H*-benzimidazole (3a)

Yield: 2.74 g (81%), mp: 291–292 °C (lit.[11] 290–291 °C). ^{1}H NMR spectrum (200 MHz, DMSO-d_6) δ 3.58 (s, 4H, CH_2), 6.40-7.45 (m, 12H, Ar-H); ^{13}C NMR spectrum (50 MHz, DMSO-d_6) δ 41.28 (CH_2), 119.23, 121.92, 127.96, 129.09, 129.42, 129.76, 135.67, 137.45 (Ar-C), 157.03 (C=N); Anal. Calcd. for $C_{22}H_{18}N_4$: C, 78.05; H, 5.32; N, 16.51. Found: C, 78.08; H, 5.36; N, 16.56.

2.2.2. 2,2'-[1,3-Phenylenedi(methylene)]bis-6-methyl-1*H*-benzimidazole) (3b)

Yield: 2.85 g (78%), mp: 154–155 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 2.38 (s, 6H, CH_3), 4.11 (s, 4H, CH_2), 6.91-7.36 (m, 10H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 21.71 (CH_3), 35.35 (CH_2), 144.46, 115.00, 123.15 (2C), 127.45 (2C), 129.08, 129.60, 130.84, 137.90, 138.37, 139.10 (Ar-C), 153.52 (C=N); Anal. Calcd. for $C_{24}H_{22}N_4$: C, 78.65; H, 6.06; N, 15.31. Found: C, 78.66; H, 6.05; N, 15.29.

2.2.3. 2,2'-[1,3-Phenylenedi(methylene)]bis-6-nitro-1*H*-benzimidazole) (3c)

Yield: 3.30 g (77%), mp: 211–212 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 4.24 (s, 4H, CH_2), 7.23-7.33 (m, 5H, Ar-H), 7.64 (s, 2H, Ar-H), 8.06 (d, J =8.4 Hz, 2H, Ar-H), 8.38 (s, 1H, Ar-H), 13.01 (s, 2H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 35.02 (CH_2), 111.35, 118.85, 121.66, 129.38 (2C), 135.50, 136.34, 143.15 (Ar-C), 154.04 (C=N); Anal. Calcd. for $C_{22}H_{16}N_6O_4$: C, 61.70; H, 3.69; N, 19.61. Found: C, 61.68; H, 3.76; N, 19.62.

2.2.4. 2,2'-[14-Phenylenedi(methylene)]bis-1*H*-benzimidazole (4a)

Yield: 2.97 g (88%), mp: 360–362 °C (lit.[11] >300 °C). ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 4.14 (s, 4H, CH_2), 7.10-7.46 (m, 12H, Ar-H), 12.21 (s, 2H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 35.05 (CH_2), 111.35, 118.85, 121.66, 129.38 (2C), 135.50, 136.34, 143.15 (Ar-C), 154.04 (C=N); Anal. Calcd. for $C_{22}H_{18}N_4$: C, 78.05; H, 5.32; N, 16.51. Found: C, 78.08; H, 5.36; N, 16.56.

2.2.5. 2,2'-[1,4-Phenylenedi(methylene)]bis-6-methyl-1*H*-benzimidazole) (4b)

Yield: 3.07 g (84%), mp: 283–285 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 2.37 (s, 6H, CH_3), 4.11 (s, 4H, CH_2), 6.93 (d, J =8.4 Hz, 2H, Ar-H), 7.26-7.35 (m, 8H, Ar-H), 12.13 (s, 2H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 21.71 (CH_3), 35.05 (CH_2), 123.08, 129.32 (4C), 130.77, 136.40 (2C) (Ar-C), 153.67 (C=N); Anal. Calcd. for $C_{24}H_{22}N_4$: C, 78.65; H, 6.06; N, 15.31. Found: C, 78.65; H, 6.06; N, 15.31.

2.2.6. 2,2'-[1,4-Phenylenedi(methylene)]bis-6-nitro-1*H*-benzimidazole) (4c)

Yield: 3.38 g (79%), mp: 301–303 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 4.24 (s, 4H, CH_2), 7.32 (s, 5H, Ar-H), 7.64 (d, J =8.8 Hz, 2H, Ar-H), 8.05 (d, J =8.8 Hz, 2H, Ar-H), 8.38 (s, 1H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 35.02 (CH_2), 117.85 (2C), 129.69 (4C), 135.75 (2C), 142.73 (2C) (Ar-C), 159.15 (C=N); Anal. Calcd. for $C_{22}H_{16}N_6O_4$: C, 61.70; H, 3.69; N, 19.61. Found: C, 61.68; H, 3.76; N, 19.62.

2.3. Synthesis of compounds 5a–5c and 6a–6c

A solution of compounds **3a–3c** or **4a–4c** (0.01 mol) in acetone (10 mL) was placed in a closed vessel and dry K_2CO_3 (0.05 mol) was added. The mixture was irradiated in a microwave at 90 °C for 5 min (hold time) with pressure control. The mixture was then cooled to room temperature and ethyl bromoacetate (0.021 mol) was added. Again, it was irradiated in a microwave at 90 °C for 10 min (hold time) at 300 W maximum power. After the reaction was completed (monitored by TLC; ethyl acetate and hexane, 3:1), the mixture was cooled and taken in a beaker, and the product was precipitated by addition of water. The product was filtrated, dried, and recrystallized from ethanol.

2.3.1. Diethyl 2,2'-[1,3-phenylenebis(methylene-1*H*-benzimidazole-2,1-diyl)]diacetate (5a)

Yield: 4.99 g (98%), mp: 181–183 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 1.11 (t, J = 6.8 Hz, 6H, CH_3), 4.01 (q, J = 6.8 Hz, 4H, OCH_2), 4.22 (s, 4H, CH_2), 5.15 (s, 4H, NCH_2), 7.13-7.20 (m, 8H, Ar-H), 7.45 (s, 2H, Ar-H), 7.59 (s, 2H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 14.35 (CH_3), 33.25 (CH_2), 44.99 (NCH_2), 61.61 (OCH_2), 110.54, 119.06, 122.08, 122.47, 127.67, 128.95, 129.87, 136.13, 137.02, 142.55 (Ar-C), 154.09 (C=N), 168.26 (C=O); Anal. Calcd. for $C_{30}H_{30}N_4O_4$: C, 70.59; H, 5.94; N, 16.96. Found: C, 70.57; H, 5.97; N, 16.97.

2.3.2. Diethyl 2,2'-{1,3-phenylenebis[methylene-6-methyl-1*H*-benzimidazole-2,1-diyl)]} diacetate (5b)

Yield: 5.00 g (93%), mp: 87–89 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 1.11 (t, J =6.8 Hz, 6H, CH_3), 2.40 (s, 6H, CH_3), 4.00 (q, J =6.8 Hz, 4H, OCH_2), 4.17 (s, 4H, CH_2), 5.09 (s, 4H, NCH_2), 6.99-7.47 (m, 10H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 14.36 (CH_3), 21.61, 21.83 (CH_3), 33.26 (CH_2), 44.88, 45.00 (NCH_2), 61.56, 61.59 (OCH_2), 110.06, 110.30, 118.67, 118.91, 123.47, 123.73, 127.56, 127.58, 128.91, 129.78, 131.02, 131.75, 134.26, 137.11, 140.69, 142.90 (Ar-C), 153.51, 153.91 (C=N), 168.27, 168.30 (C=O); Anal. Calcd. for $C_{32}H_{34}N_4O_4$: C, 71.32; H, 6.33; N, 10.42. Found: C, 71.35; H, 6.36; N, 10.40.

2.3.3. Diethyl 2,2'-{1,3-phenylenebis[methylene-6-nitro-1*H*-benzimidazole-2,1-diyl)]} diacetate (5c)

Yield: 5.34 g (89%), mp: 179–180 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 1.11 (q, J = *6.8*, 6H, CH_3), 4.01 (t, J =6.8 Hz, 4H, OCH_2), 4.29 (s, 4H, CH_2), 5.29, 5.36 (s, 4H, NCH_2), 7.17-7.26 (m, 4H, Ar-H), 7.71-7.78 (m, 2H, Ar-H), 8.11-8.16 (m, 2H, Ar-H), 8.47 (d, J =1.5 Hz, 1H, Ar-H), 8.62 (d, J =1.5 Hz, 1H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 14.31 (CH_3), 33.26 (CH_2), 45.44 (NCH_2), 61.85 (OCH_2), 108.00, 111.36, 115.23, 117.97, 118.32, 119.36, 128.01, 129.15, 130.05, 135.67, 136.31, 140.69, 141.74, 143.09, 143.31, 147.16 (Ar-C), 158.45, 159.85 (C=N), 167.74, 167.91 (C=O); Anal. Calcd. for $C_{30}H_{28}N_6O_8$: C, 60.05; H, 4.74; N, 14.02. Found: C, 60.00; H, 4.70; N, 13.99.

2.3.4. Diethyl 2,2'-[1,4-phenylenebis(methylene-1*H*-benzimidazole-2,1-diyl)]diacetate (6a)

Yield: 5.05 g (99%), mp: 345 °C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 1.05 (t, J =5.1 Hz, 6H, CH_3), 3.93 (q, J =5.1 Hz, 4H, OCH_2), 4.20 (s, 4H, CH_2), 5.13 (s, 4H, NCH_2), 7.09-7.59 (m, 12H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 14.28 (CH_3), 33.04 (CH_2), 44.93 (NCH_2), 61.56 (OCH_2), 110.51, 119.51, 121.71, 122.05, 122.43, 129.37 (3C), 135.17, 136.12, 136.33, 142.50 (Ar-C), 154.03 (C=N), 168.22 (C=O); Anal. Calcd. for $C_{30}H_{30}N_4O_4$: C, 70.54; H, 5.99; N, 16.94. Found: C, 70.57; H, 5.97; N, 16.97.

2.3.5. Diethyl 2,2'-{1,4-phenylenebis[methylene(5(6)-methyl-1*H*-benzimidazole-2,1-diyl)]} diacetate (6b)

Yield: 5.17 g (96%), mp: 248–250 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 1.05 (t, J = 6.8 Hz, 6H, CH_3), 2.39 (s, 6H, CH_3), 3.52 (q,J = 6.8 Hz, 4H, OCH_2), 4.18 (s, 4H, CH_2), 5.09 (s, 4H, NCH_2), 6.98-7.46 (m, 10H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 14.27 (CH_3), 21.60, 21.81 (CH_3), 32.89 (CH_2), 44.72, 44.83 (NCH_2), 61.55 (OCH_2), 110.04, 110.27, 118.64, 118.87, 123.49, 123.74, 129.33 (2C), 131.06, 131.77, 134.22, 135.22, 136.29, 140.68, 142.89 (Ar-C), 153.68, 154.11 (C=N), 168.25, 168.79 (C=O); Anal. Calcd. for $C_{32}H_{34}N_4O_4$: C, 71.30; H, 6.36; N, 10.45. Found: C, 71.35; H, 6.36; N, 10.40.

2.3.6. Diethyl 2,2'-{1,4-phenylenebis[methylene-6-nitro-1*H*-benzimidazole-2,1-diyl)]} diacetate (6c)

Yield: 5.46 g (91%), mp: 238–240 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 1.08 (t,J =5.1 Hz, 6H, CH_3), 3.98 (q, J =5.1 Hz, 4H, OCH_2), 4.30 (s, 4H, CH_2), 5.30 (s, 4H, NCH_2), 7.23 (s, 4H, Ar-H), 7.71-7.78 (m, 2H, Ar-H), 8.09-8.16 (m, 2H, Ar-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 14.26 (CH_3), 32.94, 33.04 (CH_2), 45.35, 45.42 (NCH_2), 61.84 (OCH_2), 108.01, 111.37, 115.22, 118.00, 118.34, 119.35, 129.60, 134.62, 135.65, 140.69, 141.77, 143.09, 143.32, 147.19 (Ar-C), 158.61, 160.01 (C=N), 167.73, 167.90 (C=O); Anal. Calcd. for $C_{30}H_{28}N_6O_8$: C, 60.02; H, 4.76; N, 14.05. Found: C, 60.00; H, 4.70; N, 13.99.

2.4. Synthesis of compounds 7a–7c and 8a–8c

A solution of compound **5a–5c** or **6a–6c** (0.01 mol) in n-butanol (10 mL) and hydrazine monohydrate (0.05 mol) was taken in a closed vessel. The mixture was irradiated in a microwave at 120 °C for 10 min (hold time) at 300 W maximum power. After the reaction was completed (monitored by TLC; ethyl acetate and hexane, 3:1), the mixture was cooled to room temperature and taken in a beaker, and a white solid appeared. This crude product was filtrated, dried, and washed with ethanol to yield the pure product.

2.4.1. 2,2'-[1,3-Phenylenebis(methylene-1*H*-benzimidazole-2,1-diyl)]diacetohydrazide (7a)

Yield: 4.00 g (83%), mp: 235–236 °C. ^{1}H NMR spectrum (200 MHz, DMSO-d_6) δ 3.54 (s, 4H, CH_2), 4.22 (s, 4H, NH_2), 4.78 (s, 4H, NCH_2), 7.15-7.56 (m, 12H, Ar-H), 9.53 (s, 2H, NH); ^{13}C NMR spectrum (50 MHz, DMSO-d_6) δ 33.60 (CH_2), 45.15 (NCH_2), 110.69, 119.22, 122.17, 122.49, 127.91, 128.25, 130.38, 136.27, 137.55, 142.87 (Ar-C), 154.76 (C=N), 166.66 (C=O); Anal. Calcd. for $C_{26}H_{26}N_8O_2$: C, 64.75; H, 5.46; N, 23.20. Found: C, 64.72; H, 5.43; N, 23.22.

2.4.2. 2,2'-{1,3-Phenylenebis[methylene-6-methyl-1*H*-benzimidazole-2,1-diyl)]} diacetohydrazide (7b)

Yield 4.34 g (86%), mp: 284–286 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 2.40 (s, 6H, CH_3), 3.44 (s, 4H, CH_2), 4.21 (s, 4H, NH_2), 4.76 (s, 4H, NCH_2), 6.98-7.44 (m, 10H, Ar-H), 9.53 (s, 2H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 21.63, 21.88 (CH_3), 33.39 (CH_2), 43.85, 44.98 (NCH_2), 110.01, 110.26, 118.60, 118.83, 123.30, 123.52, 127.60, 128.97, 130.08, 130.85, 131.48, 134.21, 136.30, 137.43, 140.75, 142.95 (Ar-C), 153.95, 154.36 (C=N), 166.45, 166.47 (C=O); Anal. Calcd. for $C_{28}H_{30}N_8O_2$: C, 65.80; H, 5.87; N, 21.89. Found: C, 65.86; H, 5.92; N, 21.95.

2.4.3. 2,2'-{1,3-Phenylenebis[methylene-6-nitro-1*H*-benzimidazole-2,1-diyl)]} diacetohydrazide (7c)

Yield: 4.63 (81%), mp: 290–293 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 4.28 (s, 4H, CH_2), 4.35 (s, 4H, NH_2), 4.95 (s, 4H, NCH_2), 7.19-7.31 (m, 4H, Ar-H), 7.60-7.74 (m, 2H, Ar-H), 8.07-8.17 (m, 2H, Ar-H), 8.44 (d, J =1.5 Hz, 1H, Ar-H), 8.52 (d, J =1.5 Hz, 1H, Ar-H), 9.57 (s, 2H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 33.41 (CH_2), 43.38 (NCH_2), 107.78, 111.21, 115.14, 117.83, 118.18, 119.26, 128.04, 129.17, 130.26, 135.62, 136.59, 140.74, 141.76, 142.90, 143.15, 147.24 (Ar-C), 158.84, 160.26 (C=N), 166.38 (C=O); Anal. Calcd. for $C_{26}H_{24}N_{10}O_6$: C, 54.50; H, 4.27; N, 24.49. Found: C, 54.54; H, 4.23; N, 24.46.

2.4.4. 2,2'-[1,4-Phenylenebis(methylene-1*H*-benzimidazole-2,1-diyl)]diacetohydrazide (8a)

Yield: 4.19 g (87%), mp: 305–308 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 3.42 (s, 4H, CH_2), 4.23 (s, 4H, NH_2), 4.81 (s, 4H, NCH_2), 7.15-7.24 (m, 8H, Ar-H), 7.42 (d, J =1.5 Hz, 2H, Ar-H), 7.55 (d, J =1.5 Hz, 2H, Ar-H), 9.51 (2H, s, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 33.03 (CH_2), 43.91 (NCH_2), 110.45, 118.99, 121.89, 122.01, 122.22, 129.48 (2C), 135.44, 136.07, 142.66 (Ar-C), 154.60 (C=N), 166.38 (C=O); Anal. Calcd. for $C_{26}H_{26}N_8O_2$: C, 64.79; H, 5.45; N, 23.26. Found: C, 64.72; H, 5.43; N, 23.22.

2.4.5. 2,2'-{1,4-Phenylenebis[methylene-6-methyl-1*H*-benzimidazole-2,1-diyl)]} diacetohydrazide (8b)

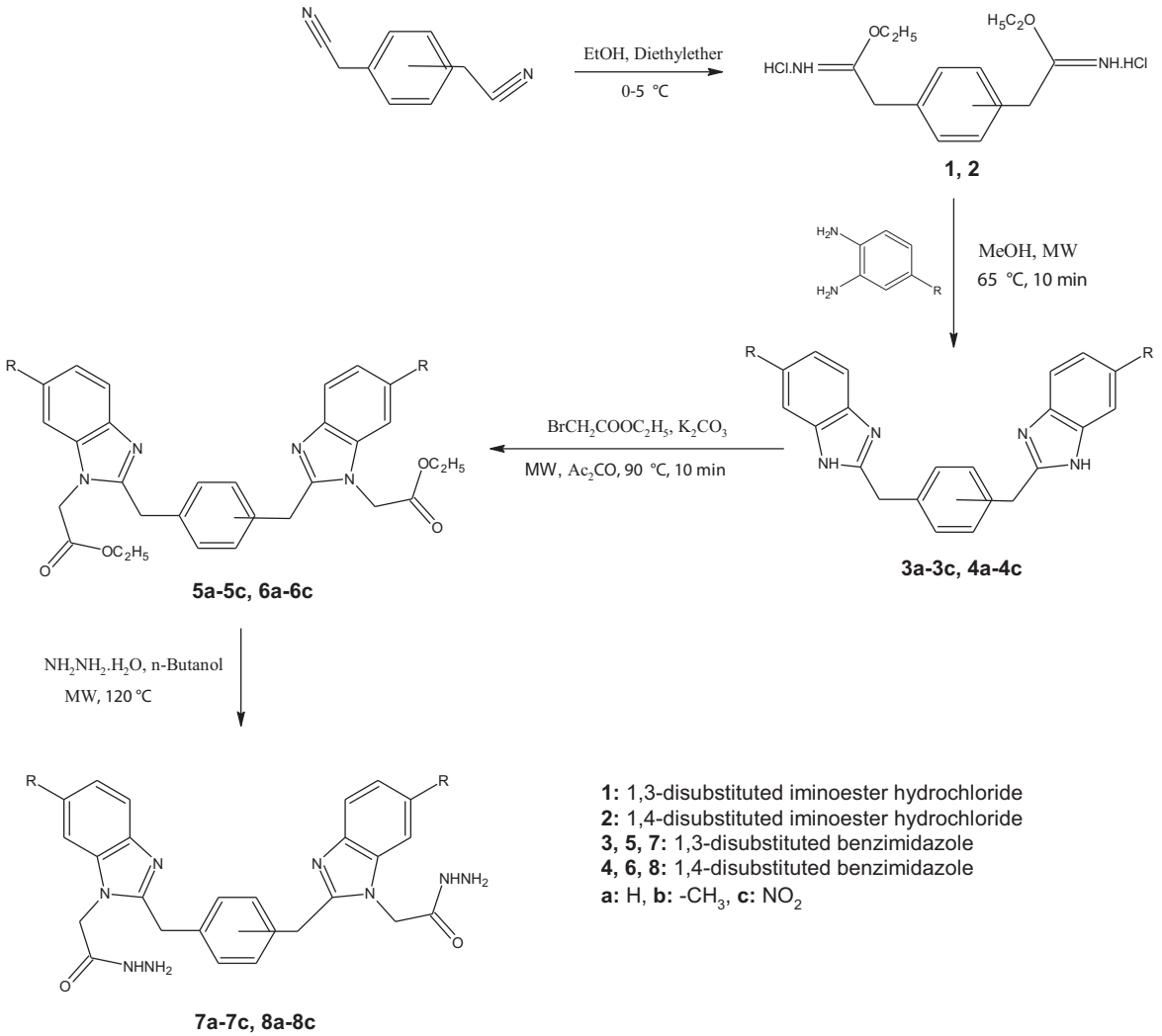
Yield: 4.28 g (84%), mp: 265–267 °C. ^{1}H NMR spectrum (200 MHz, DMSO-d_6) δ 2.34 (s, 6H, CH_3), 3.42 (s, 4H, CH_2), 4.17 (s, 4H, NH_2), 4.73 (s, 4H, NCH_2), 6.93-7.42 (m, 10H, Ar-H), 9.46 (s, 2H, NH); ^{13}C NMR spectrum (50 MHz, DMSO-d_6) δ 21.86, 22.10 (CH_3), 33.25 (CH_2), 45.00 (NCH_2), 110.23, 110.48, 118.82, 119.028, 123.52, 123.71, 129.64, 131.05, 131.66, 134.40, 135.72, 136.48, 140.98 (Ar-C), 154.28, 154.68 (C=N), 166.67 (C=O); Anal. Calcd. for $C_{28}H_{30}N_8O_2$: C, 65.80; H, 5.87; N, 21.89. Found: C, 65.83; H, 5.91; N, 21.94.

2.4.6. 2,2'-{1,4-Phenylenebis[methylene-6-nitro-1*H*-benzimidazole-2,1-diyl)]} diacetohydrazide (8c)

Yield: 4.57 g (80%), mp: 305–306 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 4.22 (s, 4H, CH_2), 4.30 (s, 4H, NH_2), 4.98 (s, 4H, NCH_2), 7.27 (s, 4H, Ar-H), 7.66-7.77 (m, 2H, Ar-H), 8.08-8.17 (m, 2H, Ar-H), 8.46 (d, J =1.5 Hz, 1H, Ar-H), 8.53 (d, 1H, J =1.5 Hz, Ar-H), 9.56 (s, 2H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ 33.11 (CH_2), 45.35 (NCH_2), 107.80, 111.23, 115.16, 117.85, 118.18, 119.26, 129.72, 134.82, 135.62, 140.77, 141.80, 142.88, 143.15, 147.29 (Ar-C), 159.00, 160.42 (C=N), 165.83, 165.91 (C=O); Anal. Calcd. for $C_{26}H_{24}N_{10}O_6$: C, 54.52; H, 4.25; N, 24.47. Found: C, 54.54; H, 4.23; N, 24.46.

3. Results and discussion

This study reports the synthesis of potential bioactive bisbenzimidazole derivatives starting from iminoester hydrochlorides and *o*-phenylenediamine derivatives. The synthetic approach is similar to the conventional method; however, this approach has not yet been applied to the synthesis of bisbenzimidazoles. Intermediate



Scheme. Synthetic route of target compounds.

iminoester hydrochlorides, compounds **1** and **2**, were synthesized according to the Pinner method.[12] They were then treated with *o*-phenylenediamine derivatives to synthesize bisbenzimidazole derivatives (**3a–3c** and **4a–4c**). The alkylation reaction of bisbenzimidazole compounds with ethyl bromoacetate gave ester derivatives (**5a–5c** and **6a–6c**). Finally, compounds **5a–5c** and **6a–6c** were treated with hydrazine monohydrate to synthesize hydrazide derivatives, which are a good intermediate for preparation of potential bioactive compounds (**7a–7c** and **8a–8c**) (Scheme).[12–16]

The chemical shift of the NH proton of bisbenzimidazole derivatives (**3a–3c** and **4a–4c**) in ^{1}H NMR is usually around 12.50 ppm. The reaction of bisbenzimidazoles with ethyl bromoacetate in the presence of dry K_2CO_3 in absolute acetone led to the formation of acetate derivatives (**5a–5c** and **6a–6c**). In addition, in ^{1}H NMR spectra a signal suggesting the presence of the NH group was not observed and the formation of new N-CH_2, OCH_2, and $-CH_3$ signals proved the alkylation of bisbenzimidazole derivatives. The ethoxy group is an easy-leaving group.[13–16] The reaction of compounds **5a–5c** and **6a–6c** with hydrazine monohydrate resulted in high yields of hydrazide derivatives **7a–c** and **8a–c**. No signals were shown belonging to $-OCH_2CH_3$, and new $-NHNH_2$ signals were formed at about 4.20 ppm (NH_2) and 9.50 ppm (NH) in ^{1}H NMR spectra. Furthermore, all NH and NH_2 signals remained with the addition of D_2O to the DMSO-d_6 solution of compounds.

4. Conclusion

This study has described a rapid and efficient protocol for the synthesis of bisbenzimidazole derivatives. Various *o*-phenylenediamine derivatives were subjected to reactions with bisiminoester hydrochlorides, providing the corresponding products in good to excellent yields under microwave heating. This method is an important alternative for the synthesis of bisbenzimidazole derivatives.

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