

Efficient microwave assisted synthesis of some new benzimidazoles containing the mebendazole nucleus

Emre Menteşe

Department of Chemistry, Art and Science Faculty, Recep Tayyip Erdogan University, 53100-Rize, Turkey

A simple and practical method has been developed for the synthesis of benzimidazoles containing the biological active mebendazole nucleus. Iminoester hydrochlorides of phenylacetic acids were used as intermediates in the reaction with 3,4-diaminobenzophenone under microwave irradiation leading to the products in good yields and in short reaction times.

Keywords: benzimidazole drug, microwave, iminoester hydrochloride, mebendazole

Benzimidazoles are an important class of biologically active heterocyclic organic compounds,¹ and their synthesis is of considerable interest. Some noteworthy biological effects of benzimidazoles include anticancer,² antihelminthic,³ antimicrobial,⁴ antihistaminic,⁵ antitumour,⁶ anti-inflammatory⁷ and antiviral⁸ activities. They are also used in various areas of chemistry and are important intermediates in organic reactions.⁹ They can also act as ligands to transition metals for modeling biological systems.¹⁰

There are many synthetic routes that have been described for the preparation of benzimidazoles containing mebendazole nucleus. The most common method for this process is using an o-phenylenediamine derivative and a carboxylic acid or an aromatic aldehyde as intermediate.^{11,12} Esters, lactones and nitriles can also produce benzimidazoles.^{12,13} However, several drawbacks are associated with these processes such as expensive reagents, harsh reaction conditions, extended reaction times, the occurrence of side products, unsatisfactory yields and complicated experimental procedures^{14–20}. Therefore, there is a need for a new short and economical synthesis of benzimidazoles containing the mebendazole nucleus.

In this study, we have developed a novel and practical method for the synthesis of benzimidazole derivatives containing the mebendazole nucleus. This method can provide a convenient way of synthesising potential bioactive benzimidazoles. The structures of new compounds were confirmed by ¹H NMR, ¹³C NMR spectroscopy and elemental analyses. The synthetic path of the target compounds is shown in Scheme 1.

Results and discussion

In this study of the synthesis of benzimidazoles, we have shown that iminoester hydrochlorides can be useful intermediates in the reaction with 3,5-diaminobenzophenone under microwave irradiation in methanol. These new heterocyclic compounds (**2a–l**) were also obtained by using conventional heating in methanol. Microwave technology has been used to synthesise benzimidazole derivatives, and important changes have been seen on the yield and reaction time.^{20–22} Using this new method, we obtained products within short reaction times and in high yields. In addition, the reaction was carried out under mild conditions. This method can provide a convenient

way of synthesising potential bioactive benzimidazoles. Comparison of the yields and reaction times under microwave irradiation and the conventional method for compounds **2a–l** are given in Table 1.

The spectra of the new compounds are accordance with their proposed structures. The ¹H NMR spectrum in DMSO-*d*₆ revealed signals at 1.70–2.25, 4.17–4.66 and 11.93–12.79 ppm (revealed by introducing D₂O) assigned to CH₃, CH₂ and NH protons, respectively. In the ¹H NMR spectra of benzimidazole derivatives, the NH signals are shown as a broad singlet at room temperature. The NH signals can be removed by deuterium exchange in DMSO-*d*₆ D₂O. Aromatic protons of benzimidazole compounds are shown as multiplet because of rapid substitution of the imidazole hydrogen between two nitrogen atoms. Thus, aromatic protons of compounds **2a–l** were observed at 7.01–8.01 ppm as multiplets. In the ¹³C NMR spectra of compounds **2a–l**, the signals for the C=N and C=O atoms appeared between 153.8–161.1 and 194.7–196.4 ppm respectively. Aromatic carbons of compounds for **2a–l** were observed at 111.9–162.9 ppm. The nuclear spin of fluorine is 1/2. This means that carbon signals are split into *n*+1 parts. One-bond ¹³C–¹⁹F coupling constants are very large, so the carbon directly bound to the fluorine will appear as a doublet with a coupling constant of ~250 Hz. Thus, these carbons in **2a–c** were observed at 162.7–165.4 and 157.8–160.5 ppm as doublet with a coupling constant of ~243 Hz. The carbons *ortho* to the fluorine were shown doublets but with much smaller couplings.

Conclusion

In conclusion, we have developed a novel and practical method has been used for the synthesis of benzimidazole derivatives containing mebendazole nucleus under microwave irradiation. This method can provide a convenient way of synthesising potential bioactive benzimidazoles.

Experimental

All the chemicals were supplied by Merck, Aldrich and Fluka. Iminoester hydrochlorides (**1a–l**) were prepared according to the Pinner method.^{24,25} Melting points were determined on capillary tubes on a Büchi oil-heated melting point apparatus and uncorrected. ¹H NMR and ¹³C NMR spectra were performed on the Varian-Mercury 200 MHz spectrometer in DMSO-*d*₆ using TMS as internal. Elemental Analyses were performed on a Carla Erba 1106 CHN analyser. A mono-mode CEM-Discover microwave was used to carry out microwave reactions in 30 mL microwave process vials with temperature control by infrared detection temperature sensor. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

Synthesis of **2a–l**

Conventional method: A mixture of corresponding iminoester hydrochlorides (**1a–l**) (0.012 mol), HCl (2 mL) and 3,5-diaminobenzophenone (0.01 mol) in dry methanol (15 mL) was placed in a round-bottomed

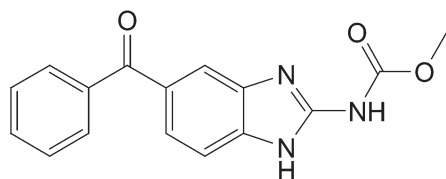
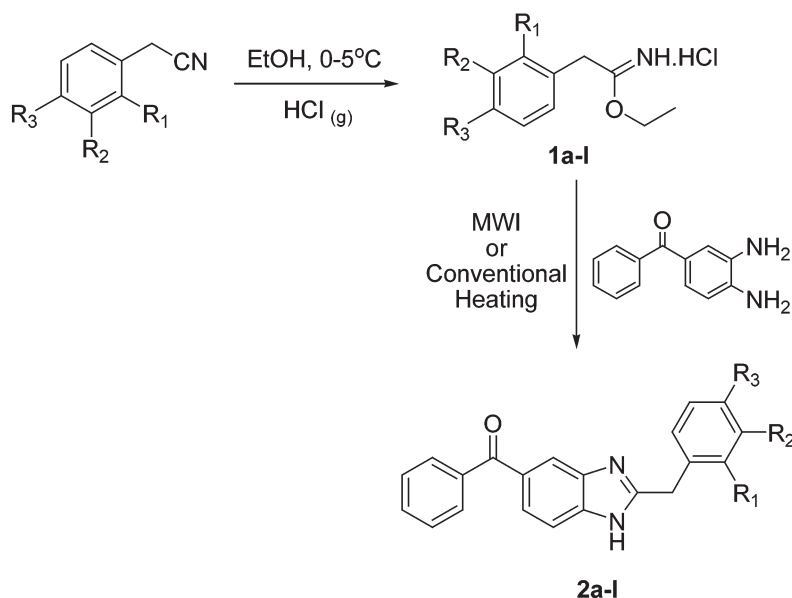


Fig. 1 Structure of mebendazole.

* Correspondent. E-mail: emre.mentese@erdogan.edu.tr



Scheme 1 The synthetic path of the target compounds **2a-l**.

Compounds	R ₁	R ₂	R ₃
2a	F	H	H
2b	H	F	H
2c	H	H	F
2d	Cl	H	H
2e	H	Cl	H
2f	H	H	Cl
2g	Br	H	H
2h	H	Br	H
2i	H	H	Br
2j	Me	H	H
2k	H	Me	H
2l	H	H	Me

Table 1 Comparison of the yields and reaction times under microwave irradiation and the conventional methods for compounds **2a-l**

Compound No.	MWI		Conventional	
	Time/min	Yield/%	Time/min	Yield/%
2a	10	84	90	75
2b	10	87	90	75
2c	10	90	90	77
2d	10	85	90	78
2e	10	88	90	79
2f	10	89	90	79
2g	10	83	90	77
2h	10	85	90	78
2i	10	91	90	78
2j	10	80	90	75
2k	10	88	90	78
2l	10	91	90	79

flask. The solution was stirred for 1.5 h at room temperature. After completion of the reaction (monitored by TLC, ethylacetate:hexane, 3:1), the mixture was poured into water and neutralised with sodium bicarbonate. The precipitate was collected by filtration and recrystallised from ethanol–water (1:3) to give pure **2a-l**.

Microwave method: A mixture of corresponding iminoester hydrochlorides (**1a-l**) (0.012 mol), HCl (2 mL) and 3,5-diaminobenzophenone (0.01 mol) in dry methanol (15 mL) was irradiated in closed vessels with pressure control at 65 °C for 10 min. (hold time) at 300 W maximum power. The above purification methods were used to give pure products **2a-l**.

Phenyl [2-(2-fluorobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2a): M.p. 185 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.09 (bs, 1H), 8.01–7.23 (m, 12H), 4.66 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 194.7, 160.2 (d, *J* = 244), 153.8, 136.8, 134.0, 133.8, 132.7, 131.8, 131.0, 130.2, 129.6, 128.5, 126.7, 124.9, 120.5 (d, *J* = 15.4), 116.0, 115.8, 114.7 (d, *J* = 61.5), 104.2, 26.1. Anal. Calcd for C₂₁H₁₅FN₂O: C, 76.35; H, 4.58; N, 8.48. Found: C, 76.37; H, 4.54; N, 8.50%.

Phenyl [2-(3-fluorobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2b): M.p. 248 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.03 (s, 1H), 8.01–7.12 (m, 12H), 4.62 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 195.5, 162.9 (d, *J* = 242.5), 155.2, 137.6, 137.0, 136.9, 134.7, 133.6, 131.8, 131.6, 131.5, 130.4, 130.3, 129.3, 127.5, 126.3, 117.1 (d, *J* = 22.3), 115.6, 115.1 (d, *J* = 61.5), 32.5. Anal. Calcd for C₂₁H₁₅FN₂O: C, 76.35; H, 4.58; N, 8.48. Found: C, 76.36; H, 4.56; N, 8.51%.

Phenyl [2-(4-fluorobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2c): M.p. 231 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 11.93 (s, 1H),

7.86–7.01 (m, 12H), 4.23 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.4, 161.7 (d, *J* = 241.3), 157.2, 139.2, 138.8, 133.9, 132.7, 131.5, 131.2, 131.1, 129.1, 124.4, 118.5, 116.2, 115.4 (d, *J* = 4), 34.7. Anal. Calcd for C₂₁H₁₅FN₂O: C, 76.35; H, 4.58; N, 8.48. Found: C, 76.38; H, 4.55; N, 8.52%.

Phenyl [2-(2-chlorobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2d): M.p. 198 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.68 (s, 1H), 7.84–7.29 (m, 12H), 4.35 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.4, 155.5, 138.8, 135.84, 134.0, 132.7, 132.3, 131.0, 130.1, 130.0, 129.6, 129.1, 128.1, 124.6, 121.9, 118.8, 114.7, 111.9, 33.6. Anal. Calcd for C₂₁H₁₅ClN₂O: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.75; H, 4.35; N, 8.04%.

Phenyl [2-(3-chlorobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2e): M.p. 231 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.01 (bs, 1H), 7.89–7.33 (m, 12H), 4.30 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.3, 156.5, 141.7, 139.8, 138.7, 138.3, 133.8, 132.8, 131.6, 131.2, 130.2, 129.5, 129.1, 128.5, 127.6, 124.8, 118.4, 115.1, 34.8. Anal. Calcd for C₂₁H₁₅ClN₂O: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.76; H, 4.34; N, 8.06%.

Phenyl [2-(4-chlorobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2f): M.p. 259 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 7.99–7.37 (m, 12H), 4.23 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.4, 156.9, 141.5, 138.8, 136.7, 132.7, 132.1, 131.5, 131.2, 130.1, 129.2, 129.1, 124.4, 118.7, 115.5, 34.9. Anal. Calcd for C₂₁H₁₅ClN₂O: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.74; H, 4.35; N, 8.10%.

Phenyl [2-(2-bromobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2g): M.p. 210 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.66 (bs, 1H), 7.86–7.24 (m, 12H), 4.37 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.4, 156.1, 138.8, 137.1, 133.3, 132.7, 132.4, 131.1, 130.2, 129.8, 129.1, 128.7, 124.9, 124.4, 118.4, 115.2, 36.2. Anal. Calcd for C₂₁H₁₅BrN₂O: C, 64.46; H, 3.86; N, 7.16. Found: C, 64.50; H, 3.84; N, 7.18%.

Phenyl [2-(3-bromobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2h): M.p. 175 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.59 (s, 1H), 7.88–7.28 (m, 12H), 4.26 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.4, 156.6, 142.7, 140.4, 139.3, 139.2, 138.8, 132.7, 132.3, 131.4, 131.2, 130.3, 130.1, 129.0, 128.7, 124.4, 122.4, 118.6, 155.1, 35.1. Anal. Calcd for C₂₁H₁₅BrN₂O: C, 64.46; H, 3.86; N, 7.16. Found: C, 64.50; H, 3.84; N, 7.18%.

Phenyl [2-(4-bromobenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2i): M.p. 189 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.72 (s, 1H), 7.87–7.29 (m, 12H), 4.26 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 196.4, 156.7, 140.5, 138.8, 132.7, 132.3, 131.4, 131.2, 130.3, 130.2, 129.1, 129.0, 128.8, 124.4, 122.4, 118.7, 155.2, 35.1. Anal. Calcd for C₂₁H₁₅BrN₂O: C, 64.46; H, 3.86; N, 7.16. Found: C, 64.45; H, 3.85; N, 7.14%.

Phenyl [2-(2-methylbenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2j): M.p. 190 °C, ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.61 (s, 1H),

7.86–7.32 (m, 12H), 4.43 (s, 2H) 1.70 (s, 3H); ^{13}C NMR (50 MHz, DMSO- d_6) δ 196.4, 161.1, 143.9, 138.8, 132.7, 131.1, 130.1, 129.3, 129.1, 128.0, 127.4, 124.3, 119.2, 40.0, 21.0. Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.99; H, 5.53; N, 8.60%.

Phenyl [2-(3-methylbenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2k): M.p. 219 °C, ^1H NMR (200 MHz, DMSO- d_6) δ 7.88–7.19 (m, 12H), 4.19 (s, 2H) 2.11 (s, 3H); ^{13}C NMR (50 MHz, DMSO- d_6) δ 196.4, 157.4, 142.6, 139.1, 138.8, 138.4, 137.6, 132.7, 131.2, 130.1, 129.2, 129.1, 128.0, 126.6, 124.4, 118.5, 115.1, 35.6, 21.7. Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.98; H, 5.54; N, 8.61%.

Phenyl [2-(4-methylbenzyl)-1H-1,3-benzimidazol-5-yl]methanone (2l): M.p. 188 °C, ^1H NMR (200 MHz, DMSO- d_6) δ 12.79 (s, 1H), 7.85–7.15 (m, 12H), 4.17 (s, 2H) 2.25 (s, 3H); ^{13}C NMR (50 MHz, DMSO- d_6) δ 196.4, 157.5, 142.7, 138.8, 134.7, 132.7, 131.1, 130.1, 129.8, 129.4, 129.1, 124.3, 118.3, 115.0, 35.3, 21.3. Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.94; H, 5.57; N, 8.60%.

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