Microwave-Assisted Synthesis of Some Benzimidazole Derivatives Containing Imine Function

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Abstract
Benzimidazole is an important pharmacophore in modern drug discovery. Many benzimidazole derivatives have been synthesized by organic chemists to obtain new drug candidates. In this work, seven new benzimidazole derivatives containing imine function have been synthesized by using microwave irradiation and conventional heating procedure. The results showed that microwave heating has many advantages on classical heating procedure on yields, purity of product and reduced times.

Keywords: Benzimidazole, Schiff base, Microwave irradiation, Imine function

1. Introduction
Benzimidazoles are heterocyclic aromatic organic compounds. These compounds are bicyclic in nature which consists benzene and imidazole (Barker et al. 1960). The use of benzimidazole dates many years back (Patil et al. 2008). In 1990 various benzimidazole derivatives were synthesized with substitution of floline, propylene and tetrahydroquinoline . These new compounds resulted in increased stability, biological activity and bioavailability (Kubo et al. 1990; Uchida et al. 1990). So, some benzimidazole drugs used in both human and veterinary medicine (Velik et al. 2004) such as anti-inflammatory (Kulkarni et al. 2013), analgesic (Achar et al. 2010), antimicrobial (Son et al. 2012), antitumor (Gowda et al. 2009), anticancer (Rashid et al. 2012), antibacterial (Tuncbilek et al. 2009), antihypertensive (Wang et al. 2012), protein kinase inhibitory (Sarno et al. 2011), antitubercular activity (Kumar et al. 2011), lipase inhibition (Menteşe et al. 2014), anti urease (Bekircan et al. 2014). Because of these biological and pharmacological activities, nowadays there has been an increasing interest in the chemistry of imidazole fused benzimidazoles (Chen et al. 2011). There are some ways to synthesis of benzimidazoles. In recent years synthetic methods have been used but because of poor yields, use of expensive reagents and long reaction time need more economical and environmental conditions (Dawood et al. 2011; Varma 2012). The use of microwave irradiation for synthesis; the reaction rates, the yields of products can be increased (Kappe 2004). Because of these reasons many benzimidazole derivatives have been synthesised with microwave irradiation (Yilmaz et al. 2013).

In this work, we have synthesized some benzimidazole derivatives containing imine function by using microwave irradiation and conventional heating procedure. The yields of these two methods were compared.

2. Result and Discussion
In this study, we have synthesized some benzimidazole derivatives containing imine function by using microwave heating and conventional procedures. Firstly, compound 1, ethyl imido-p-bromophenylacetate hydrochloride, was prepared according to the literature (Kalıveci 2005). Then, this compound (1) was treated with o-phenylenediamine in methanol to synthesize 2-(4-bromobenzyl)-1H-benzimidazole (2). The compound 2 was treated with ethyl bromoacetate in acetone with dry K₂CO₃ to synthesize ethyl [2-(4-bromobenzyl)-1H-benzimidazol-1-yl]acetate (3). Ethoxy group is an easy leaving group. Treatment of compound 3 with hydrazine monohydrate in ethanol gave 2-[2-(4-bromobenzyl)-1H-benzimidazol-1-yl]acetohydrazide (4) (Scheme 1.) (Menteşe et al. 2015).
Scheme 1. Synthesis of compound 4

After the synthesis of compound 4, this compound was treated with 7 different aromatic aldehyde to synthesize benzimidazole derivatives containing imine function, compounds 5a-g.

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Scheme 2. Synthesis of compounds 5a-g

The structure of these compounds were identified by Infrared (IR) and Proton Nuclear Magnetic Resonance (¹H-NMR) spectroscopy data. IR spectra of these compounds gave NH band between 3109-3204 cm⁻¹, C=O band between 1687-1709 cm⁻¹ and C=N band between 1602-1660 cm⁻¹. ¹H-NMR spectra of compounds 5a-g gave the correct signals with proposed structures. NH signals were shown at about 11.50 ppm, N=CH signals were shown between 8.00-9.00 ppm and NCH₂ signals were shown between 5.00-5.50 ppm. When ¹H-NMR spectra of these compounds have been compared, it has been seen that some of the protons have 2 sets of signal at different ppm. This is because of the compounds, which have arylene-hydrazide structure, exist as E/Z geometrical isomer from C=N double bond and cis/trans amide conformer at the CO-NH single bond. According to the literature (Kahveci et al. 2014), compounds which have C=N double bond prefers E geometrical isomer in DMSO-d₆ and Z isomers can be preferred in less polar solvents. N-CH₂ and N-H signals were observed 2 sets of signals because of cis/trans conformer. The ratio in each case has been calculated by using ¹H-NMR data. E/Z and cis/trans geometrical isomer of compounds 5a-g and selected ¹H-NMR spectrum has been given in scheme 3 and figure 1.

Scheme 3. E/Z geometrical isomer and cis/trans amid conformer of compounds 5a-g
3. Experimental

All the chemicals were supplied from Merck, Aldrich and Fluka. Melting points were taken on capillary tubes on a Büchi oil heated melting point apparatus and are uncorrected. $^1$H-NMR spectra were recorded on a Varian-Mercury 400 MHz spectrometer (DMSO-d$_6$ as solvent, TMS as internal standard). A mono mode CEM-Discover Microwave was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in microwave process vials (30 mL) with control of the temperature by infrared detection temperature sensor. It was monitored by a computer and maintained constant at a constant value by a discrete modulation of delivered microwave power. After completion of the reaction, the vial was cooled to 60 °C via air jet cooling.

Synthesis of Compounds 5a-g

Method A (Conventional): A mixture of compound 4 (0.01 mol) and corresponding aromatic aldehyde (0.01 mol) in ethanol/acetic acid (10/1 mL) was refluxed for 5 hours. After the reaction was completed (monitored by TLC, ethyl acetate/hexane, 3:1), the crude product was formed. This product was washed with hot ethanol, filtered off and dried.

Method B (Microwave): A mixture of compound 4 (0.01 mol) and corresponding aromatic aldehyde (0.01 mol) in acetic acid (0.5 mL) was irradiated in microwave oven for 5 min. at 130 °C and 300 watt maximum microwave power. After the reaction was completed, above purification method was applied.

2-[2-(4-Bromobenzyl)-1H-benzimidazol-1-yl]-N'-(2-hydroxyphenyl)methylidene]acetohydrazide (5a)

Yield: % 65 (for conventional method), % 86 (for microwave method) mp: 290-291 ºC, IR (KBr) cm$^{-1}$: 3290 (OH), 3182 (NH), 1698 (C=O), 1621 (C=N). $^1$H-NMR (400 MHz, DMSO-d$_6$): δ 4.21+4.26 (s, 2H, CH$_2$), 5.03+5.44 (s, 2H, NCH$_2$, trans and cis amid conformer, cis/trans ratio 59/41), 6.86-6.93 (m, 2H, Ar-H), 7.14-7.28 (m, 5H, Ar-H), 7.44-7.58 (m, 4H, Ar-H), 7.76-7.78 (m, 1H, Ar-H), 10.05+10.88 (s, 1H, OH), 11.66+11.95 (s, 1H, NH).

2-[2-(4-Bromobenzyl)-1H-benzimidazol-1-yl]-N'[(4-chlorophenyl)methylidene]acetohydrazide (5b)

Yield: % 60 (for conventional method), % 82 (for microwave method) mp: 270-271 ºC, IR (KBr) cm$^{-1}$: 3128 (NH), 1695 (C=O), 1606 (C=N). $^1$H-NMR (400 MHz, DMSO-d$_6$): δ 4.22+4.26 (s, 2H, CH$_2$), 5.03+5.47 (s, 2H, NCH$_2$, trans and cis amid conformer, cis/trans ratio 73/27), 7.16-7.28 (m, 4H, Ar-H), 7.43-7.59 (m, 6H, Ar-H), 7.70-7.78 (m, 2H, Ar-H), 8.04-8.23 (s, 1H, CH, E/Z geometrical isomer, E/Z ratio 72/28), 11.81+11.88 (s, 1H, NH).

2-[2-(4-Bromobenzyl)-1H-benzimidazol-1-yl]-N'-(4-bromophenyl)methylidene]acetohydrazide (5c)

Yield: % 64 (for conventional method), % 84 (for microwave method) mp: 272-273 ºC, IR (KBr) cm$^{-1}$: 3182 (NH), 1695 (C=O), 1609 (C=N). $^1$H-NMR (400 MHz, DMSO-d$_6$): δ 4.22+4.25 (s, 2H, CH$_2$), 5.01+5.46 (s, 2H, NCH$_2$,
trans and cis amid conformer, cis/trans ratio 71/29), 7.14-7.24 (m, 4H, Ar-H), 7.43-7.58 (m, 6H, Ar-H), 7.69-7.76 (m, 2H, Ar-H), 8.05+8.23 (s, 1H, CH, E/Z geometrical isomer, E/Z ratio 75/25), 11.74+11.81 (s, 1H, NH).

2-[2-(4-Bromobenzyl)-1H-benimidazol-1-yl]-N-\([\{(4\text{-dimethylamino})phenyl\}methylidene]\) acetoacrylaldehyde (5d)

Yield: % 70 (for conventional method), % 92 (for microwave method) mp: 275-276 °C, IR (KBr) cm\(^{-1}\): 3204 (NH), 1687 (C=O), 1614 (C=N). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): δ 4.23+4.27 (s, 2H, CH\(_2\)), 4.98+5.42 (s, 2H, NCH\(_2\)), trans and cis amid conformer, cis/trans ratio 75/25), 6.69-7.64 (m, 2H, Ar-H), 7.15-7.29 (m, 4H, Ar-H), 7.42-7.60 (m, 6H, Ar-H), 7.95+8.11 (s, 1H, CH, E/Z geometrical isomer, E/Z ratio 69/31), 11.49+11.56 (s, 1H, NH).

2-[2-(4-Bromobenzyl)-1H-benimidazol-1-yl]-N-\([\{(4\text{-chloro-2-hydroxyphenyl})methylidene]\}) acetoacrylaldehyde (5e)

Yield: % 70 (for conventional method), % 92 (for microwave method) mp: 267-268 °C, IR (KBr) cm\(^{-1}\): 3350 (OH), 3185 (NH), 1702 (C=O), 1660 (C=N). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): δ 4.21+4.26 (s, 2H, CH\(_2\)), 5.03+5.49 (s, 2H, NCH\(_2\)), trans and cis amid conformer, cis/trans ratio 64/36), 6.92-7.83 (m, 12H, Ar-H+CH\(_2\)), 8.31+8.42 (s, 1H, OH), 11.73 (s, 1H, NH).

2-[2-(4-Bromobenzyl)-1H-benimidazol-1-yl]-N-\([\{(3\text{-bromo-2-hydroxyphenyl})methylidene}\}) acetoacrylaldehyde (5f)

Yield: % 70 (for conventional method), % 92 (for microwave method) mp: 272-273 °C, IR (KBr) cm\(^{-1}\): 3380 (OH), 3171 (NH), 1702 (C=O), 1659 (C=N). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): δ 4.21+4.25 (s, 2H, CH\(_2\)), 5.02+5.49 (s, 2H, NCH\(_2\)), trans and cis amid conformer, cis/trans ratio 64/36), 6.89-7.95 (m, 12H, Ar-H+CH\(_2\)), 8.29+8.41 42 (s, 1H, OH), 11.73 (s, 1H, NH).

2-[2-(4-Bromobenzyl)-1H-benimidazol-1-yl]-N-\([\{(3\text{-bromo-4-chlorophenyl})methylidene}\}) acetoacrylaldehyde (5g)

Yield: % 70 (for conventional method), % 92 (for microwave method) mp: 252-253 °C, IR (KBr) cm\(^{-1}\): 3109 (NH), 1709 (C=O), 1614 (C=N). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): δ 4.21+4.23 (s, 2H, CH\(_2\)), 5.01+5.49 (s, 2H, NCH\(_2\)), trans and cis amid conformer, cis/trans ratio 70/30), 7.13-8.19 (m, 12H, Ar-H+CH\(_2\)), 11.81+11.92 (s, 1H, NH).

4. Conclusion

It has been described an efficient method for the synthesis of benimidazole derivatives containing imine function using the microwave technology. All reactions have been carried out with conventional heating in order to compare. All compounds are new and identified by spectral data.

References


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