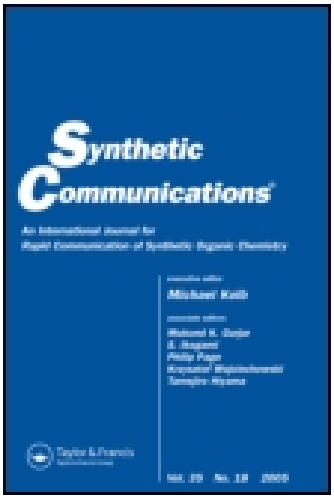

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Efficient Microwave-Assisted Synthesis of N-(2-Alkyl/aryl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamides

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EFFICIENT MICROWAVE-ASSISTED SYNTHESIS OF *N*-(2-ALKYL/ARYL-4-PHENYL-1*H*-IMIDAZOL-1-YL)-2-PHENYLACETAMIDES

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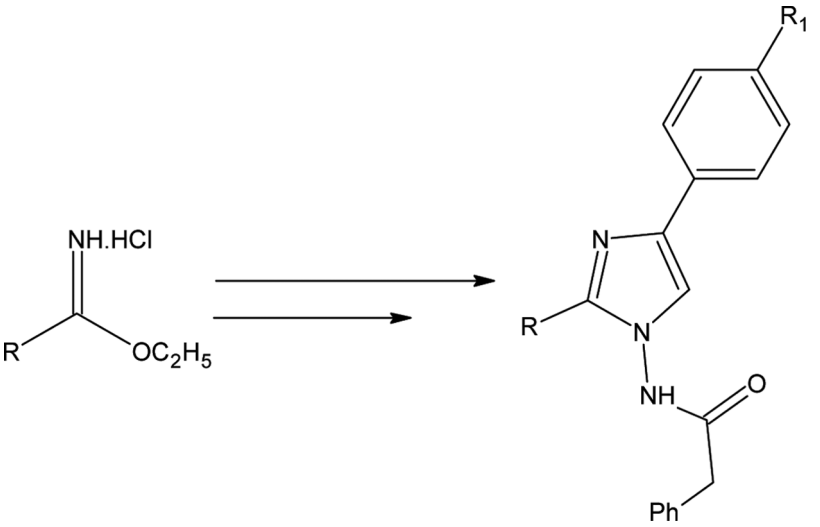
GRAPHICAL ABSTRACT



Abstract *An easy, efficient, and environmentally friendly method for the synthesis of N-(2-alkyl/aryl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamides from the reaction of phenyl acylbromides and phenylacetohydrazide derivatives has been presented. Shorter reaction times, simple workup procedure, no catalyst requirement, and use of small quantities of organic solvent are the most obvious advantages of this protocol.*

Keywords Catalyst-free reaction; imidazoles; microwave irradiation; phenylacetohydrazide; phenylacyl bromide

INTRODUCTION

Imidazole ring is an important structure in modern drug discovery.[1–4] The imidazole derivatives with different biological activities, including antimicrobial,[5]

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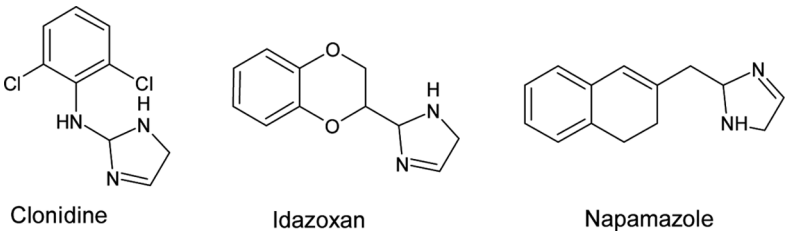


Figure 1. Structures of clonidine, idazoxan, and napamazole.

anticonvulsant,[6] anticancer,[7,8] and antiviral,[9] are present in the literature. Also, many of today's drugs include imidazole skeleton in their structure such as Clonidine (α_2 adrenergicagonist), Idazoxan, and Napamazole (antidepressant)[3,10,11] (Fig. 1).

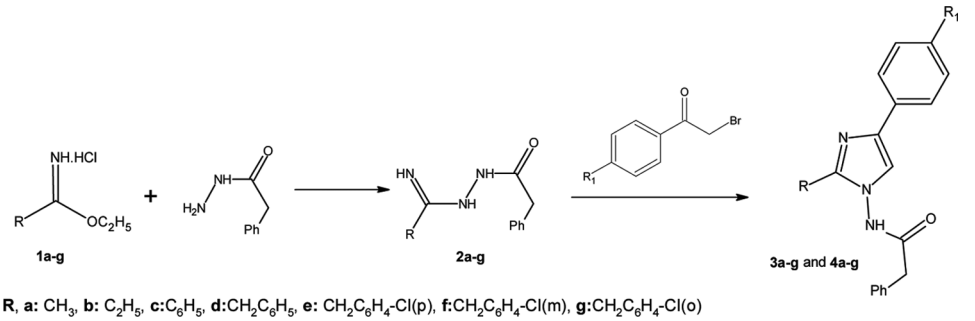
Because of their important biological properties, many imidazole derivatives have been synthesized extensively and various synthetic protocols have been developed by organic chemists.[12–15] However, there are only a few protocols found in literature for the synthesis of *N*-(2-alkyl/aryl-4-phenyl-1*H*-imidazol-1-yl)-2-phenylacetamides. These protocols require catalyst and hard purification methods.[16–18] Therefore, there is a need for an environmental and ecofriendly method for the synthesis of *N*-(2-alkyl/aryl-4-phenyl-1*H*-imidazol-1-yl)-2-phenylacetamides.

Microwave-assisted organic synthesis is an important development for organic chemistry in the 21st century. When comparing it to the conventional heating methods, it has many advantages, such as reducing reaction times, providing greater yield and purity, and requiring less energy. One of the biggest advantages of microwave heating is that it supplies environmentally friendly conditions for organic reactions. Many organic reactions can be performed in dry media instead of in organic solvent by using microwave heating.[19–21]

In literature, the general reaction conditions of imidazoles include using a considerable amount of organic solvent, some kinds of catalysts, and harsh reaction conditions.[22–24] In this study, a novel, practical, and efficient method is developed for the synthesis of *N*-(2-alkyl/aryl-4-phenyl-1*H*-imidazol-1-yl)-2-phenylacetamides by using microwave irradiation. This new method has some advantages on previously reported procedures because it provides greater yield and requires a small quantity of organic solvent.

RESULTS AND DISCUSSION

In this study, a convenient method for the synthesis of *N*-(2-alkyl/aryl-4-phenyl-1*H*-imidazol-1-yl)-2-phenylacetamides has been achieved by using microwave irradiation and catalyst-free conditions. Iminoester hydrochlorides (**1a–g**) have been synthesized according to the literature.[25] Treatment of compounds **1a–g** with phenylacetic hydrazide in the presence of NaOEt gave the hydrazide derivatives **2a–g**.[16,17] The compounds **2a–g** were reacted with phenyl acylbromide and 4-chlorophenyl acylbromide, separately, with 1 mL of acetonitrile under microwave



R, **a:** CH_3, **b:** C_2H_5, **c:**C_6H_5, **d:**$CH_2C_6H_5$, **e:** $CH_2C_6H_4$-Cl(p), **f:**$CH_2C_6H_4$-Cl(m), **g:**$CH_2C_6H_4$-Cl(o)
R_1: H (3a-g), Cl (4a-g)

Scheme 1. Synthetic route for compounds **3a–g** and **4a–g**.

irradiation (Scheme 1). Also, the compounds **3a–g** and **4a–g** have been synthesized with conventional heating procedure and results were compared to microwave heating (Table 1).

The microwave heating has provided greater yields, around 10%, compared to classical heating for the synthesis of compounds **3a–g** and **4a–g** (except for compound **3b**). The classical heating techniques are rather slow, and a temperature gradient can develop within the sample. In addition, local overheating can cause substrate and reagent decomposition. In contrast, the microwave energy is introduced into the chemical reactor and direct access by the energy source to the reaction vessel is obtained. The microwave radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be the same throughout the sample, which can lead to fewer by-products and/or decomposition products.[26]

Syntheses of compounds **3a–g** and **4a–g** were tried under solvent-free conditions but have not succeeded because of decomposition of reagents. In dry-media

Table 1. Comparison of conventional and microwave heating procedure for compounds **3a–g** and **4a–g**

	Microwave heating			Conventional heating		
Compound	Time (min)	Yield (%)	Acetonitrile (mL)	Time (h)	Yield (%)	Acetonitrile (mL)
3a	5 × 4	72	1	3	64	5
3b	5 × 4	47	1	3	62	5
3c	5 × 4	69	1	3	52	5
3d	5 × 4	66	1	3	45	5
3e	5 × 4	71	1	3	68	5
3f	5 × 4	76	1	3	64	5
3g	5 × 4	65	1	3	53	5
4a	5 × 4	78	1	3	67	5
4b	5 × 4	56	1	3	52	5
4c	5 × 4	67	1	3	60	5
4d	5 × 4	72	1	3	63	5
4e	5 × 4	76	1	3	68	5
4f	5 × 4	78	1	3	61	5
4g	5 × 4	67	1	3	56	5

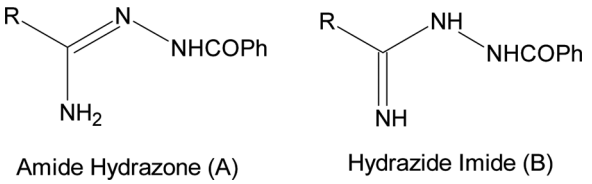
Table 2. Reaction condition for compound **3a**

Solvent	Microwave temperature (°C)	Microwave power (W)	Reaction time (min)	Yield (%)
Ethanol	100	200	5 × 5	35
Ethanol	100	150	5 × 4	37
Ethanol	100	100	5 × 4	41
Ethanol	95	200	5 × 5	38
Ethanol	95	150	5 × 5	40
Ethanol	95	100	5 × 5	16
Ethanol	90	100	5 × 6	18
Acetonitrile	100	200	5 × 3	42
Acetonitrile	100	100	5 × 3	59
Acetonitrile	95	100	5 × 3	67
Acetonitrile	90	150	5 × 4	63
Acetonitrile	**90**	**100**	**5 × 4**	**72**
Acetonitrile	85	100	5 × 5	68

reaction, the homogeneity cannot be fully guaranteed. Therefore, formation of undesirable and decomposed products decreased the reaction yield.[27] However, these compounds have been synthesized using only 1 mL of organic solvent (acetonitrile) under microwave irradiation. Even when using small quantities of organic solvent, the polarity and homogeneity for the microwave interaction have been provided. At the same time, the microwave power and the reaction temperature were very important parameters on the yield of the compounds **3a–g** and **4a–g**. More microwave power and temperature caused decomposition of the starting compounds, which is why we abstained from using greater microwave power and reaction temperature. The reaction conditions, tried for compound **3a**, have been given in Table 2.

Our literature survey has revealed that acetamidrazones have shown amide hydrazone (A)-hydrazide imide (B) tautomerism and they could exist as *E* and *Z* isomers because of the C=N bond (Scheme 2).[28] When we investigated ^{1}H NMR and ^{13}C NMR spectra of compounds **2a–g**, some proton and carbon atoms have two set of signals coming from this tautomerism. In ^{1}H NMR spectra of compounds **2a–g**, the signals between 10.44 and 9.43 ppm had NH protons and those between 6.68 and 6.19 ppm have NH_2 protons (amide hydrazone A). In ^{13}C NMR spectra of compounds **2a–g**, C=O and C=N carbons have signals at about 170 and 152 ppm, respectively.

^{1}H NMR and ^{13}C NMR spectra of compounds **3a–g** and **4a–g** have given compatible signals with the proposed structures. NH and CH_2 protons have been observed at 13.53–11.26 ppm and 4.27–3.51 ppm and C=O and C=N carbons have been seen at about 170 and 148 ppm, respectively. The aromatic carbons of



Scheme 2. Amidehydrazone (A) and hydrazide imide (B) structures.

compounds **3a–g** and **4a–g** were observed between 142.2 and 113.8 ppm. In our previously works, it has been proved that the compounds that have CO-NH single bond could exist in *cis*/*trans* amide conformer. That is why, when aromatic carbons of compounds **3a–g** and **4a–g** have been compared with their structures, the number of these aromatic carbons could be seen more than proposed.[29]

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 and ^{13}C NMR spectra were recorded on a Varian-Mercury 400-MHz spectrophotometer (solvent DMSO-d_6, tetramethylsilane [TMS] as internal standard). The mass spectra were recorded on Thermo Scientific Quantum Access max liquid chromatography–mass spectrometry (LC-MS) instrument. A monomode 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 N-(2-Alkyl/aryl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamides (3a–g and 4a–g)

Conventional method. A solution of compounds **2a–g** (0.01 mol) in acetonitrile (5 mL) and phenylacyl bromide or 4-chlorophenylacyl bromide (0.013 mol) was placed in a round-bottom flask. The mixture was refluxed for 3 h. After the completion of the reaction, (monitored by thin-layer chromatography [TLC], ethyl acetate/hexane, 3:2), the mixture was cooled to room temperature. The formed gel-like mixture was extracted with acetone (4 × 5 mL) and filtered off. Then, diethyl ether was added to the filtrate to precipitate the desired products **3a–g** and **4a–g**.

Microwave method. A mixture of compounds **2a–g** (0.01 mol), phenylacyl bromide or 4-chlorophenyl acylbromide (0.013 mol), and acetonitrile (1 mL) was taken in a microwave process vial and irradiated in microwave at 90 °C for 5 × 4 min at 100 W. After the completion of the reaction, (monitored by TLC, ethyl acetate/hexane, 3:2), the mixture was extracted with acetone (4 × 5 mL) and filtered off. Then, diethyl ether was added the filtrate to precipitate the desired product **3a–g** and **4a–g**.

***N*-(2-Methyl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamide (3a).** Mp 228–226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.59 (1H, br, NH); 7.74 (2H, d, $J = 7.6$, Ar-H); 7.62 (1H, s, Ar-H); 7.38–7.19 (8H, m, Ar-H); 3.67 (2H, s, CH_2); 2.12 (3H, s, CH_3). ^{13}C NMR (100 MHZ, DMSO-d_6), δ ppm: 169.8 (C=O); 145.1 (C=N); 137.1; 135.3; 134.6; 130.1; 129.6; 128.9; 127.3; 126.7; 124.5; 117.2 (Ar-C); 40.5 (CH_2); 11.8 (CH_3). LC-MS: 292 $[M+H]^+$.

***N*-[4-(4-Chlorophenyl)-2-methyl-1H-imidazol-1-yl]-2-phenylacetamide (4a).** Mp 241–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.60 (1H, s, NH);

7.78 (2H, d, $J = 6.8$, Ar-H); 7.69 (1H, s, Ar-H); 7.40–7.36 (7H, m, Ar-H); 3.67 (2H, s, CH_2); 2.11 (3H, s, CH_3). ^{13}C NMR (100 MHZ, DMSO-d_6), δ ppm: 169.9 (C=O); 145.3 (C=N); 135.9; 135.2; 133.4; 131.6; 131.0; 129.8; 129.5; 129.0; 128.9; 127.3; 126.2; 117.8 (Ar-C); 40.6 (CH_2); 11.8 (CH_3). LC-MS: 328/326 $[M+H]^+$.

CONCLUSION

A series of some novel imidazole derivatives (**3a–g** and **4a–g**) have been synthesized from the reaction of phenylacetohydrazide and phenyl acylbromide derivatives by using microwave irradiation. The microwave irradiation technique has been first used for the synthesis of *N*-(2-alkyl/aryl-4-phenyl-1*H*-imidazol-1-yl)-2-phenylacetamides (**3a–g** and **4a–g**). This technique has provided some advantages on yields and reaction times. The use of a low amount of organic solvent is very important for this reaction to ensure homogeneous reaction medium. We strongly believe that this novel technique will have a wide range of applications and we have high expectations for the synthesis of bioactive imidazole derivatives.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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