An Efficient Microwave Assisted Synthesis of *N*-(2-Alkyl/Aryl-4-Phenyl-1*H*-imidazol-1-yl)-2-phenylacetamides

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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. ¹H-NMR and ¹³C-NMR spectra were recorded on a Varian-Mercury 400 MHz spectrophotometer (solvent DMSO-d₆, TMS as internal standard). The mass spectra were recorded on Thermo Scientific Quantum Access max LC- MS spectrofotometer. 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 phenylacetohydrazide (2a-g):

A solution of sodium ethoxy (0.23 g, 0.01 mol) in absolute ethanol (25 mL) was stirred for 20 min. at room temperature and allowed to cool to 0 °C. Then, corresponding iminoester hydrochloride (0.01 mol) (**1a-g**) was gradually added; the precipitated sodium chloride was removed via filtration, and the filtrate was treated with phenylacetic hydrazide (1.50 g, 0.01 mol) at room temperature. The mixture was stirred overnight. The precipitate was filtrated off and washed with diethyl ether to obtain the pure product **2a-g**.

Spectral Data:

N'-Ethanimidoyl-2-phenylacetohydrazide (2a). yield: 78%, Mp. 169-170 °C, (168-169 °C^[1]). ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 9.64 and 9.46 (1H, s, NH, *E/Z* isomers), 7.13-7.42 (5H, m, Ar-H), 6.16 (2H, s, NH₂), 2.15 (3H, s, CH₃). ¹³C-NMR (100 MHz, DMSO-d₆), δ

ppm: 170.14; 165.23 (C=O); 154.53; 147.19 (C=N); 138.47; 130.28; 129.69; 129.45; 129.33; 128.15(Ar-C); 19.23 (CH₃).

2-Phenyl-N'-propanimidoylaceto-hydrazide (2b). yield: 52 %, Mp.156-158 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 9.73 (1H, s, NH); 7.29-7.02 (5H, m, Ar-H); 6.19 (2H, s, NH₂); 3.85 (2H, s, CH₂); 2.57 (2H, q, *J*=7.2, CH₂CH₃); 1.12 (3H, t, *J*=7.2, CH₂CH₃). ¹³C-NMR (100 MHZ, DMSO-d₆), δ ppm: 165.9 (C=O); 155.7 (C=N); 137.6; 135.2; 132.1; 128.3; 126.5 (Ar-C), 39.1 (CH₂); 27.3 (CH₂CH₃); 11.8 (CH₂CH₃).

N'-[Imino(phenyl)methyl]-2-phenylaceto-hydrazide (2c). yield: 74%, Mp.176-178 °C (176-177 °C^[1]). H-NMR (400 MHz, DMSO-d₆) δ ppm: 8.60 (1H, br, NH); 7.49-7.13 (10H, m, Ar-H); 6.87 (br, 2H, NH₂). ¹³C-NMR (100 MHZ, DMSO-d₆), δ ppm: 163.84; 163.71 (C=O); 151.13; 148.44 (C=N); 134.28; 132.26; 130.89; 129.98; 128.41; 124.20; 118.07; 115.23, 117.94 (Ar-C).

2-Phenyl-N'-(2-phenylethanimidoyl)aceto-hydrazide (2d). yield: 63%, Mp. 180-182 °C (182-183 °C^[1]). H-NMR (400 MHz, DMSO-d₆) δ ppm: 9.68 (1H, br, NH); 7.90 (s, 2H, Ar-H); 7.43-7.12 (8H, m, Ar-H); 6.41 (2H, br, NH₂); 3.57 (2H, s, CH₂). ¹³C-NMR (100 MHZ, DMSO-d₆), δ ppm: 166.31; 165.57 (C=O); 153.29; 148.32, (C=N); 134.29; 132.89; 131.29; 129.12; 127.38; 123.36; 120.41; 118.19; 117.28; 41.19 (Ar-C).

N'-[2-(4-Chlorophenyl)ethanimidoyl]-2-phenylaceto-hydrazide (2e). yield: 84%, Mp. 196-198 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 10.44 and 9.45 (1H, s, NH E/Z isomers); 7.37-7.17 (9H, m, Ar-H); 6.68 and 6.23 (2H, s, NH₂ E/Z isomers); 3.73 (2H, s, CH₂); 3.54 (2H, s, CH₂). ¹³C-NMR (100 MHZ, DMSO-d₆), δ ppm: 171.7+166.8 (C=O E/Z isomers), 152.6+147.9 (C=N E/Z isomers); 137.5; 137.0; 136.8; 131.5; 131.1; 131.0; 129.8; 128.6; 128.4; 126.7 (C=N) ; 41.1 (CH₂) ; 39.4 (CH₂).

N'-[2-(3-Chlorophenyl)ethanimidoyl]-2-phenylaceto-hydrazide (2f). yield: 84%, Mp. 196-198 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 9.63 and 9.48 (1H, s, NH E/Z isomers); 7.39-7.19 (9H, m, Ar-H); 6.26 and 6.21 (2H, s, NH₂ E/Z isomers); 3.73 (2H, s, CH₂); 3.36 (2H, s, CH₂). ¹³C-NMR (100 MHZ, DMSO-d₆), δ ppm: 171.7+166.0 (C=O E/Z isomers), 153.5+147.6 (C=N E/Z isomers); 140.8; 136.8; 133.2; 130.4; 129.8; 129.5; 129.1; 128.9; 128.6; 128.4; 127.8; 126.7; 126.5 (Ar-C); 41.6 (CH₂); 39.1 (CH₂).

N'-[2-(2-Chlorophenyl)ethanimidoyl]-2-phenylacetohydrazide (2g). yield: 76%, Mp. 192-194 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 9.65 and 9.51 (1H, s, NH E/Z isomers); 7.46-7.03 (9H, m, Ar-H); 6.23 and 6.21 (2H, s, NH₂ E/Z isomers); 3.57 (2H, s, CH₂); 3.42 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 171.7+165.8 (C=O E/Z isomers); 153.0+146.5 (C=N E/Z isomers); 137.0; 135.8; 134.0; 131.7; 130.9; 129.8; 129.5; 129.3; 128.6; 128.3; 127.5; 126.6 (Ar-C); 41.6+39.1 (CH₂, E/Z isomers); 37.7 (CH₂).

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 phenylacetyl bromide or 4-chlorophenylacetyl bromide (0.013 mol) were placed in a round-bottom flask. The mixture was refluxed for 3 hours. After the completion of the reaction, (monitored by TLC, ethyl acetate: hexane, 3:2), the mixture was cooled to room temperature. The formed gel-like mixture was extracted with acetone (4x5 mL) and filtrated off. Then, diethyl ether was added the filtrate to precipitate the desired product **3a-g** and **4a-g**.

Microwave Method: A mixture of compounds **2a-g** (0.01 mol), phenylacetyl bromide or 4-chlorophenyl acylbromide (0.013 mol) and acetonitrile (1 mL) was taken in a microwave process vial and it was irradiated in microwave at 90 °C for 5x4min. at 100 W. After the completion of the reaction, (monitored by TLC, ethyl acetate: hexane, 3:2), the mixture was extracted with acetone (4x5 mL) and filtrated off. Then, diethyl ether was added the filtrate to precipitate the desired product **3a-g** and **4a-g**.

Spectral Data:

N-(2-Methyl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamide (3a). Mp. 228-226 °C. ¹H-NMR (400 MHz, DMSO-d₆) 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, CH₂); 2.12 (3H, s, CH₃). ¹³C-NMR (100 MHz, DMSO-d₆) 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 (CH₂); 11.8 (CH₃). LC-MS: 292.20 [M+H]⁺.

N-(2-Ethyl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamide (3b). Mp. 215-217 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.60 (1H, s, NH); 7.82 (2H, d, *J*=6.4, Ar-H); 7.73 (1H, s, Ar-H); 7.46-7.30 (8H, m, Ar-H); 3.69 (2H, s, CH₂); 2.44 (2H, q, *J*=7.2, CH₂CH₃); 1.17 (3H, t, *J*=7.2, CH₂CH₃). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.3 (C=O); 146.6

(C=N); 137.4; 136.2; 136.0; 133.6; 132.2; 129.7; 129.3; 129.2; 127.3; 126.8; 126.0; 116.7 (Ar-C); 40.6 (CH₂); 33.5 (CH₂CH₃); 11.8 (CH₂CH₃). LC-MS: 306.34 [M+H]⁺.

***N*-(2,4-Diphenyl-1H-imidazol-1-yl)-2-phenylacetamide (3c).** Mp. 223-225 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.67 (1H, s, NH); 8.40 (1H, s, Ar-H); 7.96-7.86 (2H, m, Ar-H); 7.72-7.50 (2H, m, Ar-H); 7.35 (1H, s, Ar-H); 7.33-7.22 (5H, m, Ar-H); 7.19-7.03 (4H, m, Ar-H); 3.67 (s, 2H, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 171.5 (C=O); 147.2 (C=N); 138.5; 137.6; 137.1; 136.4; 136.2; 133.5; 133.1; 132.8; 131.2; 130.1; 129.5; 129.2; 127.3; 126.8; 126.4; 126.3; 115.3 (Ar-C); 41.2 (CH₂). LC-MS: 354.18 [M+H]⁺.

***N*-(2-Benzyl-4-phenyl-1H-imidazol-1-yl)-2-phenylacetamide (3d).** Mp. 241-243 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 13.53 (1H, s, NH); 7.31-6.48 (16H, m, Ar-H); 4.03 (2H, s, CH₂); 3.92 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.2 (C=O); 148.0 (C=N); 138.3; 137.5; 136.8; 136.1; 134.6; 134.0; 132.2; 131.3; 130.0; 129.8; 129.1; 128.0; 126.3; 126.0; 124.6; 113.8 (Ar-C); 42.6 (CH₂); 30.5 (CH₂). LC-MS: 368.07 [M+H]⁺.

***N*-[2-(4-Chlorobenzyl)-4-phenyl-1H-imidazol-1-yl]-2-phenylacetamide (3e).** Mp. 260-262 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.65 (1H, s, NH); 7.76 (1H, s, Ar-H); 7.70 (1H, s, Ar-H); 7.49-7.13 (13H, m, Ar-H); 3.93 (2H, s, CH₂); 3.62 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.3 (C=O); 146.8 (C=N); 135.4; 134.6; 133.9; 133.6; 132.2; 131.6; 131.1; 130.3; 130.1; 130.0; 129.7; 128.9; 128.3; 128.1; 127.5; 120.4 (Ar-C); 40.7 (CH₂); 34.5 (CH₂). LC-MS: 404.68/403.83 [M+H]⁺.

***N*-[2-(3-Chlorobenzyl)-4-phenyl-1H-imidazol-1-yl]-2-phenylacetamide (3f).** Mp. 254-256 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.62 (1H, s, NH); 7.82 (1H, s, Ar-H); 7.76 (1H, s, Ar-H); 7.67 (2H, d, *J*=6.8, Ar-H); 7.36-7.07 (11H, m, Ar-H); 3.86 (2H, s, CH₂); 3.57 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 171.5 (C=O); 147.2 (C=N); 136.2; 135.3; 134.2; 132.9; 132.0; 131.7; 131.0; 130.8; 130.4; 130.0; 129.1; 128.8; 128.6; 128.1; 127.3; 120.1 (Ar-C); 41.2 (CH₂); 35.6 (CH₂). LC-MS: 404.29/403.61 [M+H]⁺.

***N*-[2-(2-Chlorobenzyl)-4-phenyl-1H-imidazol-1-yl]-2-phenylacetamide (3g).** Mp. 261-263 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.49 (1H, s, NH); 7.61-7.09 (15H, m, Ar-H); 4.11 (2H, s, CH₂); 3.62 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.6 (C=O); 147.7 (C=N); 135.8; 135.4; 134.3; 133.9; 132.7; 132.3; 132.2; 131.9; 131.4; 130.4; 130.1;

129.2; 128.2; 127.8; 127.6; 120.5 (Ar-C); 41.1 (CH₂); 34.8 (CH₂). LC-MS: 404.53/403.66 [M+H]⁺.

***N*-[4-(4-Chlorophenyl)-2-methyl-1H-imidazol-1-yl]-2-phenylacetamide (4a).** Mp. 241-242 °C. ¹H-NMR (400 MHz, DMSO-d₆) 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, CH₂); 2.11 (3H, s, CH₃). ¹³C-NMR (100 MHz, DMSO-d₆) 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 (CH₂); 11.8 (CH₃). LC-MS: 327.80/325.95 [M+H]⁺.

***N*-[4-(4-Chlorophenyl)-2-ethyl-1H-imidazol-1-yl]-2-phenylacetamide (4b).** Mp. 229-231 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.26 (1H, s, NH); 7.97 (2H, d, *J*=6.8, Ar-H); 7.29 (1H, s, Ar-H); 7.46-7.16 (7H, m, Ar-H); 3.73 (2H, s, CH₂); 2.49 (2H, q, *J*=7.6, CH₂CH₃); 1.14 (3H, t, *J*=7.4, CH₂CH₃). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.8 (C=O); 146.5 (C=N); 138.4; 136.6; 135.6; 133.3; 131.6; 129.7; 129.5; 129.0; 127.1; 126.5; 124.8; 116.3 (Ar-C); 41.2 (CH₂); 35.2 (CH₂CH₃); 12.1 (CH₂CH₃). LC-MS: 341.12/339.98 [M+H]⁺.

***N*-[4-(Chlorophenyl)-2-phenyl-1H-imidazol-1-yl]-2-phenylacetamide (4c).** Mp. 235-237 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.56 (1H, s, NH); 8.15 (1H, s, Ar-H); 7.91-7.82 (2H, m, Ar-H); 7.76-7.41 (2H, m, Ar-H); 7.36 (2H, s, Ar-H); 7.29-7.21 (5H, m, Ar-H); 7.18-7.10 (3H, m, Ar-H); 3.67 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.8 (C=O); 148.1 (C=N); 139.3; 138.1; 137.6; 136.3; 136.1; 133.8; 133.0; 132.5; 131.0; 130.5; 128.4; 127.1; 126.0; 125.2; 124.1; 122.0; 112.9 (Ar-C); 41.0 (CH₂). LC-MS: 389.06/387.94 [M+H]⁺.

***N*-[4-(Chlorophenyl)-2-benzyl-1H-imidazol-1-yl]-2-phenylacetamide (4d).** Mp. 254-256 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.99 (1H, s, NH); 7.90 (1H, s, Ar-H); 7.48-7.46 (2H, m, Ar-H); 7.25-7.21 (2H, m, Ar-H); 7.06-6.83 (10H, m, Ar-H); 3.83 (2H, s, CH₂); 3.58 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.2 (C=O); 148.1 (C=N); 139.7; 138.7; 137.2; 136.9; 136.5; 133.3; 133.1; 132.2; 131.6; 130.3; 128.0; 127.2; 126.3; 125.1; 124.3; 122.5; 112.3 (Ar-C); 40.7 (CH₂); 30.3 (CH₂). LC-MS: 403.90/401.87 [M+H]⁺.

***N*-[2-(4-Chlorobenzyl)-4-(4-chlorophenyl)-1H-imidazol-1-yl]-2-phenylacetamide (4e).**
Mp. 262-264 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.92 (2H, s, NH); 8.30 (1H, s, Ar-H); 7.89-7.85 (4H, m, Ar-H); 7.54-7.13 (9H, m, Ar-H); 4.27 (2H, s, CH₂); 3.90 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.1 (C=O); 147.2 (C=N); 140.1; 138.2; 137.5; 136.3; 135.0; 133.8; 133.0; 131.8; 131.3; 130.2; 128.5; 127.3; 126.2; 125.0; 124.6; 122.2; 112.1 (Ar-C); 40.7 (CH₂); 30.6 (CH₂). LC-MS: 438.11/436.83 [M+H]⁺.

***N*-[2-(3-Chlorobenzyl)-4-(4-chlorophenyl)-1H-imidazol-1-yl]-2-phenylacetamide (4f).**
Mp. 260-262 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.70 (2H, s, NH); 7.45-7.13 (14H, m, Ar-H); 3.79 (2H, s, CH₂); 3.51 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.4 (C=O); 148.5 (C=N); 141.6; 139.1; 137.2; 136.5; 135.4; 133.6; 133.0; 131.3; 131.0; 130.0; 128.7; 127.5; 126.8; 125.7; 124.1; 112.7 (Ar-C); 41.2 (CH₂); 30.8 (CH₂). LC-MS: 438.02/436.96 [M+H]⁺.

***N*-[2-(2-Chlorobenzyl)-4-(4-chlorophenyl)-1H-imidazol-1-yl]-2-phenylacetamide (4g).**
Mp. 245-247 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 11.65 (1H, s, NH); 7.76-7.70 (2H, m, Ar-H); 7.49-7.23 (12H, m, Ar-H); 3.94 (2H, s, CH₂); 3.62 (2H, s, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ ppm: 170.1 (C=O); 149.9 (C=N); 142.2; 139.6; 138.1; 137.2; 136.0; 133.5; 132.3; 131.0; 130.7; 128.8; 127.8; 126.7; 125.3; 124.0; 112.6 (Ar-C); 41.3 (CH₂); 30.6 (CH₂). LC-MS: 437.91/435.88 [M+H]⁺.

REFERENCE

1. Postovskii, I. Y.; Vereshchagina, N. N. *Zhurnal Obshchei Khimii* **1959**, 29, 2139.

LC-MS Spectrum of compound **3a**

¹H-NMR Spectrum of compound **3d**

¹³C-NMR Spectrum of compound **3d**

LC-MS Spectrum of compound **3d**

¹H-NMR Spectrum of compound **3g**

¹³C-NMR Spectrum of compound **3g**

240613-IH73 #50-54 RT: 0.39-0.42 AV: 5 SB: 22 0.30-0.37, 0.14-0.23 NL: 2.87E7
T: + p ESI Q1MS [200.070-500.000]

LC-MS Spectrum of compound **3g**

¹H-NMR Spectrum of compound **4a**

¹³C-NMR Spectrum of compound **4a**

LC-MS Spectrum of compound **4a**

^1H -NMR Spectrum of compound **4d**

^{13}C -NMR Spectrum of compound **4d**

310513-imidazolH3 #70-77 RT: 0.56-0.62 AV: 8 SB: 68 0.64-0.85, 0.22-0.55 NL: 1.01E7
T: + p ESI Q1MS [200.070-750.000]

LC-MS Spectrum of compound **4d**

^1H -NMR Spectrum of compound **4g**

^{13}C -NMR Spectrum of compound **4g**

LC-MS Spectrum of compound **4g**