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Comparative study of microwave-assisted and conventional synthesis of ibuprofen-based acyl hydrazone derivatives

Ayşe UZGÖREN BARAN*
Department of Chemistry, Faculty of Science, Hacettepe University, Ankara, Turkey

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Abstract: A series of potential biological active acyl hydrazone derivatives containing ibuprofen moiety (compounds **4a**–**4p**) was synthesized by the condensation of ibuprofen hydrazone with aromatic aldehydes using conventional and microwave irradiation methods. The microwave method was found to be successful with nearly the same or higher yields and shorter reaction time, and it was more environmentally friendly compared to the conventional heating method. The chemical structures of the synthesized compounds were characterized by IR, ^{1}H NMR, and APT-NMR spectroscopy.

Key words: Ibuprofen, hydrazone, microwave, acyl hydrazones

1. Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of a number of arthritic diseases. It is thought to exhibit its anti-inflammatory activity through the inhibition of prostaglandin synthesis by blocking COX activity. Unfortunately, it causes some side effects such as gastrointestinal hemorrhage, ulceration, and decreased renal function.[1–3] Most NSAIDs have –COOH groups in their structure. This –COOH group is thought to be responsible for the gastrointestinal side effects.

Therefore, the development of more effective and safer anti-inflammatory drugs is needed. One of the strategies adopted to minimize the side effects of NSAIDs includes the synthesis of new, safer, and potent hybrid compound-containing NSAIDs.[4] In our previous work, we synthesized some new compounds by combining ibuprofen with thiazolo[3,2-b]-1,2,4-triazole ring. Our results also revealed that hybrid compounds lead to less gastric toxicity in vivo.[5]

In addition, hydrazones and their derivatives are attractive targets for researchers worldwide due to their widespread applications in biology and medicinal chemistry, exhibiting potential therapeutic properties such as antibacterial–antifungal,[6–8] anticonvulsant,[9–11] anti-inflammatory,[12,13] antimalarial,[14] and antituberculosis activities.[15–19] Hydrazones are not only important compounds for drug design, but they are also important compounds as possible ligands for metal complexes, organocatalysis, and for the synthesis of heterocyclic compounds.[20] The ease of preparation, increased hydrolytic stability relative to imines, and tendency toward crystallinity are all desirable characteristics of hydrazones.[21–23] Due to these positive traits, hydrazones have been under study for a long time.

Hydrazone derivatives derived from anti-inflammatory agents have been studied in the literature.[24] Diclofenac acid-based hydrazones have shown antimycobacterial activities,[20] while ibuprofen- and naproxen-

*Correspondence: uzgoren@hacettepe.edu.tr

based hydrazones have shown cytotoxic activity against human prostate cancer (Pc-3) cell lines in vitro.[24] The same study results show that ibuprofen-based hydrazones show cytotoxicity superior to that of naproxen. A synthetic method for the preparation of ibuprofen-based acyl hydrazones needs longer reaction time and more organic solvent.

In the light of these studies, it is worthwhile to synthesize some ibuprofen-based hybrid compounds in order to improve its safety profile while maintaining full anti-inflammatory/analgesic and cytotoxic activity. In the present study, some acylhydrazone compounds carrying ibuprofen residue were synthesized using both conventional and microwave synthesis methods. Some known ibuprofen-based acyl hydrazone derivatives were also synthesized using the microwave method. The present report provides an extended study of the chemistry of these compounds and a comparison between microwave-assisted and conventional heating methods.

2. Experimental section

Ibuprofen was kindly supplied by Atabay Pharmaceuticals. Microwave irradiation was carried out in a microwave oven (Milestone-RotaPREP). All the microwave-assisted reactions were carried out in closed Teflon microwave vessels at constant microwave power and at variable temperature. All chemicals were from Aldrich Chemical Co. Melting points were measured in sealed tubes using an electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a Thermo Scientific Nicolet iS10 spectrometer. Elemental analyses were performed by Thermo Finnigan Flash EA 1112 CHN analyzer. ^{13}C and ^{1}H NMR spectra were obtained by a Bruker DPX-400, 400 MHz High Performance Digital FT-NMR Spectrometer using DMSO-d_6. All chemical shift values were recorded in δ (ppm). Chemical shift (δ) values of rotameric hydrogens whenever identified are presented within parentheses by assigning an asterisk (*) along with that of the other form. The purity of the compounds was checked by thin layer chromatography on silica gel-coated aluminum sheets. Compounds **3**, **4a**, **4b**, **4d**, **4g**, and **4m** are already known in the literature.[24] Conventional synthesis of these compounds was carried out using the reported procedure.[24] Except for compound **4o**, the compounds have CAS Registry Numbers but they have no reference, analytical, or spectral data; therefore the analytical and spectral data for unknown products are described next.

2.1. 2-(4-i-Butylphenyl)-propionic acid hydrazide 3; general procedure

2.1.1. Microwave method

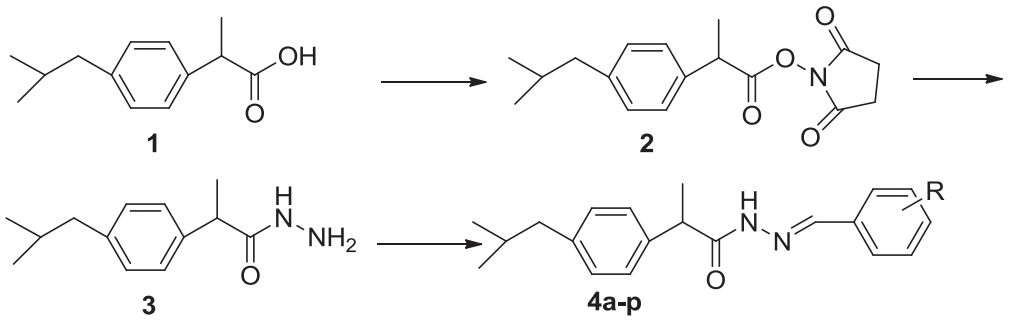
A mixture of 2-(4-i-butylphenyl)-propionic acid ester, **2** (1 g, 3.3 mmol), and hydrazine hydrate (3.0 mL, 61.73 mmol) in 3 mL of ethanol was placed in Teflon microwave vessels. The system was heated in a microwave oven for 40 min at 100-W constant MW power and at variable temperature. After completion of the reaction (TLC monitoring using ethyl acetate), the residue was treated with water. The separated solid was filtered and dried to give the desired product **3** (Scheme).

2.2. Acyl hydrazones 4a–4p; general procedure

2.2.1. Conventional method

To a stirred solution of 2-(4-*i*-butylphenyl)-propionic acid hydrazide (0.5 g, 2.3 mmol) in ethanol (30 mL), various aldehydes (2.3 mmol) were added, after which the mixture was heated at 90–95 °C until completion of the reaction (TLC monitoring using ethyl acetate and n-hexane (3:1)). The mixture was cooled to room

temperature and the solvent was removed by rotary evaporator. The residue was treated with water. The separated solid was filtered and dried to give the desired products **4a**–**4p**.



Scheme. Synthetic pathways of ibuprofen-based acyl hydrazone derivatives.

2.2.2. Microwave method

A mixture of 2-(4-*i*-butylphenyl)-propionic acid hydrazide (0.5 g, 2.3 mmol) and various aldehydes (2.3 mmol) in 3 mL of ethanol was placed in Teflon microwave vessels. The system was heated in a microwave oven for various times at 100 W. After completion of the reaction (TLC monitoring using ethyl acetate and n-hexane (3:1)), the residue was treated with water. The solid separated was filtered and dried to give the desired product **4a–4p.**

2-(4-i-Butylphenyl)-propionic acid (3-chloro-benzylidene)-hydrazide (4c). White solid, yield 78% (conventional); 90% (microwave), mp 144.5–145.7 °C. IR (ν_{max}, cm^{-1}): 3207, 3063, 2966, 2898, 2865, 1661 (C = O), 1605 (CN), 1563 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, J 6.56 Hz, $CH(CH_3)_2$), 1.40 (1.38*, 3H, d, $CHCH_3$), 1.76–1.82 (1H, m, $CH(CH_3)_2$), 2.41 (2.38*, 2H, d, J7.17 Hz, $CHCH_2$), 4.62 (3.67*, 1H, q, J7.10 Hz, $CHCH_3$), 7.07–7.63 (ArH, m, 7CH), 7.71 (7.67*, ArH, s, CH), 8.18 (7.89*, 1H, s, CH), 11.62 (11.35*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.9, 19.0, 22.6, 30.0, 30.1, 31.2, 40.9, 44.1, 44.7, 125.9, 126.0, 126.4, 126.8, 127.5, 127.7, 129.3, 129.4, 129.7, 130.0, 131.1, 134.0, 134.1, 137.0, 139.2, 139.7, 140.1, 141.3, 145.3, 170.5, 175.7. Anal. calcd. for $C_{20}H_{23}ClN_2O$: C, 70.05; H, 6.77; N, 8.17. Found: C, 70.12; H, 6.80; N, 8.15.

2-(4-i-Butylphenyl)-propionic acid (2-bromo-benzylidene)-hydrazide (4e). White solid, yield 86% (conventional); 92% (microwave), mp 137.2–138.0 °C. IR (ν_{max}, cm^{-1}): 3184, 3051, 2954, 2854, 1660 (C = O), 1568, 1511 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, J 6.55 Hz, $CH(CH_3)_2$), 1.40 (1.38*, 3H, d, $CHCH_3$), 1.74–1.83 (1H, m, $CH(CH_3)_2$), 2.41 (2.37*, 2H, d, J7.11 Hz, $CHCH_2$), 4.63 (3.66*, 1H, q, J6.90 Hz, $CHCH_3$), 7.07–7.91 (ArH, m, 8CH), 8.54 (8.27*, 1H, s, CH), 11.76 (11.48*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.9, 19.0, 22.6, 30.0, 30.1, 40.8, 44.2, 44.7, 123.7, 123.9, 127.4, 127.5, 127.6, 127.7, 128.5, 129.4, 129.4, 131.8, 132.1, 133.4, 133.5, 133.6, 139.1, 139.6, 139.7, 140.1, 141.4, 145.2, 170.5, 175.7. Anal. calcd. for $C_{20}H_{23}BrN_2O$: C, 62.00; H, 5.99; N, 7.24. Found: C, 60.65; H, 5.73; N, 7.11

2-(4-i-Butylphenyl)-propionic acid (3-bromo-benzylidene)-hydrazide (4f). White solid, yield 89% (conventional); 95% (microwave), mp 157.0–158.0 °C. IR (ν_{max}, cm^{-1}): 3196, 3081, 2954, 2859, 2842, 1667 (C = O), 1604 (CN), 1562, 1508 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, $CH(CH_3)_2$), 1.39 (1.37*, 3H, d, J 7.49 Hz, $CHCH_3$), 1.74–1.84 (1H, m, $CH(CH_3)_2$), 2.41 (2.38*, 2H, d, J7.12 Hz, $CHCH_2$), 4.60 (3.67*, 1H, q, J7.42 Hz, $CHCH_3$), 7.07–7.67 (ArH, m, 7CH), 7.87 (7.81*, ArH, s, 1CH), 8.15 (7.87*, 1H, s, CH), 11.65 (11.37*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.9, 19.0, 22.6, 30.0, 30.1, 40.9, 44.1,

44.7, 122.5, 122.6, 126.3, 126.5, 127.5, 127.7, 129.3, 129.4, 129.4, 129.6, 131.4, 132.6, 132.9, 137.2, 137.3, 139.2, 139.6, 139.7, 140.1, 141.2, 145.2, 170.5, 175.7. Anal. calcd. for $C_{20}H_{23}BrN_2O$: C, 62.00; H, 5.99; N, 7.24. Found: C, 60.29; H, 6.05; N, 7.14.

2-(4-i-Butylphenyl)-propionic acid (2-fluoro-benzylidene)-hydrazide (4h). White solid, yield 80% (conventional); 91% (microwave), mp 159.0–160.0 °C. IR (ν_{max}, cm^{-1}): 3172, 3084, 2952, 2913, 2854, 1670 (C = O), 1609 (CN) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, J 6.57 Hz, $CH(CH_3)_2$), 1.40 (1.38*, 3H, d, $CHCH_3$), 1.74–1.82 (1H, m, $CH(CH_3)_2$), 2.41 (2.38*, 2H, d, J7.01 Hz, $CHCH_2$), 4.64 (3.64*, 1H, q, J6.67 Hz, $CHCH_3$), 7.07–7.90 (ArH, m, 8CH), 8.43 (8.13*, 1H, s, CH), 11.66 (11.39*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ 18.9, 19.0, 22.6, 30.0, 30.1, 40.8, 44.1, 44.7, 112.9, 113.1, 113.3, 113.6, 116.8, 117.0, 117.2, 123.6, 123.7, 127.5, 127.7, 129.4, 131.3, 131.4, 137.3, 139.2, 139.7, 140.1, 141.6, 145.6, 161.7, 164.0, 170.5, 175.7. Anal. calcd. for $C_{20}H_{23}FN_2O$: C, 73.58; H, 7.11; N, 8.59. Found: C, 72.76; H, 6.99; N, 8.49.

2-(4-i-Butylphenyl)-propionic acid (3-fluoro-benzylidene)-hydrazide (4i). White solid, yield 93% (conventional); 94% (microwave), mp 130.5–132.0 °C. IR (ν_{max}, cm^{-1}): 3187, 3063, 2929, 2848, 1663 (C = O), 1602 (CN), 1575, 1509 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.86 (0.82*, 6H, d, J 6.59 Hz, $CH(CH_3)_2$), 1.39 (1.38*, 3H, d, $CHCH_3$), 1.74–1.82 (1H, m, $CH(CH_3)_2$), 2.41 (2.38*, 2H, d, J7.08 Hz, $CHCH_2$), 4.63 (3.67*, 1H, q, J7.22 Hz, $CHCH_3$), 7.07–7.52 (ArH, m, 8CH), 8.21 (7.91*, 1H, s, CH), 11.60 (11.35*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.9, 19.0, 22.6, 30.0, 30.1, 40.7, 44.2, 44.7, 116.3, 116.4, 116.5, 116.6, 122.1, 122.2, 122.3, 125.4, 126.6, 126.7, 127.5, 127.7, 129.4, 129.5, 132.0, 132.1, 132.3, 132.4, 135.8, 135.9, 139.1, 139.5, 139.6, 139.7, 140.1, 159.8, 159.9, 162.3, 162.4, 170.4, 175.7. Anal. calcd. for $C_{20}H_{23}FN_2O$: C, 73.58; H, 7.11; N, 8.59. Found: C, 73.04; H, 7.35; N, 8.54.

2-(4-i-Butylphenyl)-propionic acid (4-fluoro-benzylidene)-hydrazide (4j). White solid, yield 74% (conventional; 93% (microwave), mp 139.1–141.0 °C. IR (ν_{max}, cm^{-1}): 3210, 3066, 2963, 2910, 2842, 1655 (C = O), 1602 (CN), 1560, 1506 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, J 6.60 Hz, $CH(CH_3)_2$), 1.39 (1.37*, 3H, d, $CHCH_3$), 1.72–1.85 (1H, m, $CH(CH_3)_2$), 2.41 (2.37*, 2H, d, J 7.10 Hz, $CHCH_2$), 4.64 (3.66*, 1H, q, J 6.99 Hz, $CHCH_3$), 7.06–7.74 (ArH, m, 8CH), 8.20 (7.91*, 1H, s, CH), 11.52 (11.27*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.3, 18.5, 22.1, 29.5, 29.6, 40.2, 43.6, 44.2, 115.6, 115.7, 115.8, 115.9, 127.0, 127.2, 128.7, 128.8, 128.9, 128.9, 129.0, 129.1, 130.8, 130.9, 138.8, 139.1, 139.2, 139.5, 141.4, 145.4, 161.6, 161.8, 164.0, 164.2, 169.8, 175.1. Anal. calcd. for $C_{20}H_{23}FN_2O$: C, 73.58; H, 7.11; N, 8.59. Found: C, 73.02; H, 7.39; N, 8.77.

2-(4-i-Butylphenyl)-propionic acid (2-methoxy-benzylidene)-hydrazide (4k). White solid, yield 78% (conventional); 91% (microwave), mp 136.3–137.1 °C. IR (ν_{max}, cm^{-1}): 3193, 3069, 2957, 2919, 2877, 2836, 1650 (C = O), 1596 (CN), 1549, 1512 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, J 6.71 Hz, $CH(CH_3)_2$), 1.39 (1.37*, 3H, d, $CHCH_3$), 1.72–1.85 (1H, m, $CH(CH_3)_2$), 2.40 (2.37*, 2H, d, J7.10 Hz, $CHCH_2$), 3.84 (3.81*, 3H, s, OCH_3), 4.64 (3.63*, 1H, q, J7.12 Hz, $CHCH_3$), 6.97–7.81 (ArH, m, 8CH), 8.55 (8.26*, 1H, s, CH), 11.51 (11.22*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ 18.8, 18.9, 22.6, 30.0, 30.1, 40.7, 44.2, 44.7, 56.0, 56.1, 112.2, 121.1, 121.2, 122.7, 122.8, 125.7, 125.8, 127.5, 127.7, 129.3, 129.4, 131.5, 131.9, 138.6, 139.3, 139.6, 139.7, 140.1, 142.4, 158.0, 170.1, 175.5. Anal. calcd. for $C_{21}H_{26}N_2O_2$: C, 74.51; H, 7.75; N, 8.28. Found: C, 74.00; H, 7.69; N, 8.47.

2-(4-i-Butylphenyl)-propionic acid (3-methoxy-benzylidene)-hydrazide (4l). White solid, yield 81% (conventional); 90% (microwave), mp 115.9–142.7 °C. IR (ν_{max}, cm^{-1}): 3172, 3072, 2952, 2860, 2827,

1667 (C = O), 1600 (CN), 1575, 1508 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, 6H, d, J 6.60 Hz, $CH(CH_3)_2$), 1.39 (1.37*, 3H, d, $CHCH_3$), 1.74–1.83 (1H, m, $CH(CH_3)_2$), 2.41 (2.38*, 2H, d, J7.02 Hz, $CHCH_2$), 3.81 (3.78*, 3H, s, OCH_3), 4.62 (3.66*, 1H, q, J6.91 Hz, $CHCH_3$), 6.96–7.36 (ArH, m, 8CH), 8.17 (7.87*, 1H, s, CH), 11.51 (11.26*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.4, 18.6, 22.1, 29.5, 29.6, 40.4, 43.6, 44.2, 55.0, 55.1, 110.7, 111.1, 115.8, 116.0, 119.5, 119.9, 127.0, 127.2, 128.9, 129.8, 129.9, 135.6, 135.7, 138.7, 139.2, 139.3, 139.5, 142.2, 146.4, 159.4, 159.5, 169.9, 175.0. Anal. calcd. for $C_{21}H_{26}N_2O_2$: C, 74.51; H, 7.75; N, 8.28. Found: C, 73.58; H, 7.54; N, 8.26.

2-(4-i-Butylphenyl)-propionic acid (2-methyl-benzylidene)-hydrazide (4n). White solid, yield 86% (conventional); 92% (microwave), mp 147.5–148.6 °C. IR (ν_{max}, cm^{-1}): 3187, 3040, 2954, 2922, 2869, 1655 (C = O), 1614 (CN), 1557, 1507 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.86 (0.83*, 6H, d, J 6.62 Hz, $CH(CH_3)_2$), 1.40 (1.38*, 3H, d, $CHCH_3$), 1.71–1.85 (1H, m, $CH(CH_3)_2$), 2.40 (2.37*, 3H, s, CH_3), 2.41 (2.38*, 2H, d, J7.27 Hz, $CHCH_2$), 4.63 (3.65*, 1H, q, J6.85 Hz, $CHCH_3$), 7.07–7.76 (ArH, m, 8CH), 8.45 (8.21*, 1H, s, CH), 11.49 (11.18*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 19.0, 19.1, 19.5, 19.7, 22.6, 22.7, 30.0, 30.1, 44.2, 44.7, 126.2, 126.4, 126.6, 126.7, 127.5, 127.7, 129.3, 129.4, 129.8, 130.1, 131.3, 131.4, 132.7, 136.9, 137.2, 139.3, 139.6, 139.7, 140.1, 142.2, 145.5, 170.2, 175.5. Anal. calcd. for $C_{21}H_{26}N_2O$: C, 78.21; H, 8.13; N, 8.69. Found: C, 77.87; H, 7.95; N, 8.57

2-(4-i-Butylphenyl)-propionic acid (3-methyl-benzylidene)-hydrazide (4o). White solid, yield 78% (conventional; 96% (microwave), mp 128.5–129.5 °C. IR (ν_{max}, cm^{-1}): 3202, 3092, 2969, 2895, 2877, 1678 (C = O), 1607 (CN), 1576, 1510 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.82*, d, 6H,J 6.59 Hz, $CH(CH_3)_2$), 1.39 (1.38*, 3H, d, $CHCH_3$), 1.75–1.84 (1H, m, $CH(CH_3)_2$), 2.34 (2.33*, 3H, s, CH_3), 2.41 (2.38*, 2H, d, J7.20 Hz, $CHCH_2$), 4.63 (3.65*, 1H, q, J7.23 Hz, $CHCH_3$), 7.07–7.48 (ArH, m, 8CH), 8.15 (7.88*, 1H, s, CH), 11.47 (11.22*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.4, 20.8, 20.9, 22.1, 22.2, 24.4, 25.3, 29.5, 29.6, 40.2, 43.6, 44.2, 123.9, 124.3, 127.0, 127.1, 127.2, 128.6, 128.7, 128.8, 128.9, 130.3, 130.6, 134.2, 134.3, 137.9, 138.0, 138.8, 139.1, 139.2, 139.5, 142.6, 146.5, 169.8, 175.0. Anal. calcd. for $C_{21}H_{26}N_2O$: C, 78.21; H, 8.13; N, 8.69. Found: C, 78.48; H, 8.02; N, 7.92.

2-(4-i-Butylphenyl)-propionic acid (4-methyl-benzylidene)-hydrazide (4p). White solid, yield 92% (conventional); 96% (microwave), mp 152.2–152.8 °C. IR (ν_{max}, cm^{-1}): 3193, 3060, 2960, 2854, 2842, 1658 (C = O), 1607 (CN), 1552, 1507 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 (0.83*, 6H, d, J 6.61 Hz, $CH(CH_3)_2$), 1.39 (1.37*, 3H, d, $CHCH_3$), 1.75–1.84 (1H, m, $CH(CH_3)_2$), 2.33 (3H, s, CH_3), 2.41 (2.38*, 2H, d, J 7.07 Hz, $CHCH_2$), 4.64 (3.65*, 1H, q, J6.71 Hz, $CHCH_3$), 7.06–7.56 (ArH, m, 8CH), 8.15 (7.88*, 1H, s, CH), 11.43 (11.17*, 1H, s, NH). APT-NMR (100 MHz, DMSO): δ = 18.4, 20.9, 22.1, 22.2, 29.5, 29.6, 40.1, 43.6, 44.2, 126.6, 26.9, 127.0, 127.3, 128.8, 128.9, 129.3, 129.4, 131.5, 131.6, 138.8, 139.1, 139.2, 139.4, 139.5, 139.7, 142.6, 146.5, 169.7, 175.0. Anal. calcd. for $C_{21}H_{26}N_2O$: C, 78.21; H, 8.13; N, 8.69. Found: C, 78.38; H, 8.07; N, 8.73.

3. Results and discussion

In this study, inspired by previous studies on hydrazones and ibuprofen, and recent trends of using environmentally friendly techniques, a green method to synthesize a series of ibuprofen-based acyl hydrazones in the minimum amount of ethanol was developed under microwave irradiation, which is a new method for these derivatives, from arylaldehyde and ibuprofen hydrazide (Scheme). Additionally, the unknown compounds, **4c**, **4e**, **4f**, **4h**, **4i**, **4j**, **4k**, **4l**, **4n**, **4o**, and **4p**, were synthesized by conventional heating procedures in order to

compare the results of conventional and microwave-assisted methods. The yield and time data for compounds **4a**, **4b**, **4d**, **4g**, and **4m** are taken from the literature.[22,24]

The starting compound, 2,5-dioxopyrrolidin-1-yl-2-(4-isobutylphenyl)propanoate (**2**), was prepared according to a published procedure.[25]

The 2-(4-i-butylphenyl)-propionic acid hydrazide (**3**) was prepared by reacting **2** with hydrazine hydrate in ethanol under microwave-assisted heating as well as conventional heating (Scheme). The reaction was carried out using 1.0 g (3.3 mmol) of **2** and 3 mL (61.73 mmol) of hydrazine hydrate with the conventional method requiring about 8 h in 30 mL of absolute alcohol, while the microwave irradiation method required only 40 min in 3 mL of absolute ethanol. In the conventional method the yields are lower compared to microwave irradiation.

The MWI power was optimized by carrying out the experiment at 50 W, 100 W, 200 W, 300 W, and 400 W for 5 min in the synthesis of **3**. The results showed that the yield of product **3** was improved as the MWI power increased from 50 W to 100 W but as the MWI power increased continuously, the yield of the products decreased. Therefore, 100 W was chosen for the further reactions (Figure 1).

To optimize the reaction time, the reaction was carried out for 5 min to 50 min at 100 W. The results show that the reaction at 40 min gave the best yield (Figure 2).

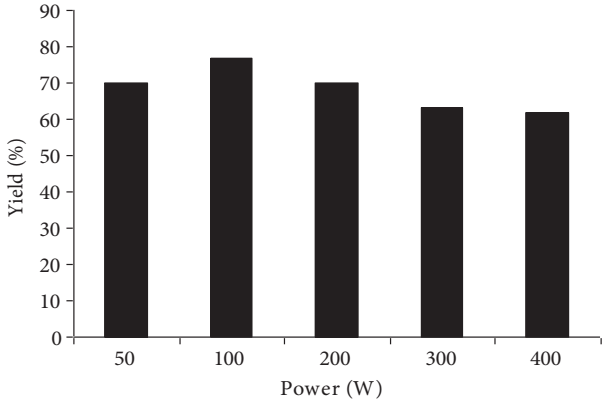


Figure 1. Effect of MWI power on the yield of compound **3**.

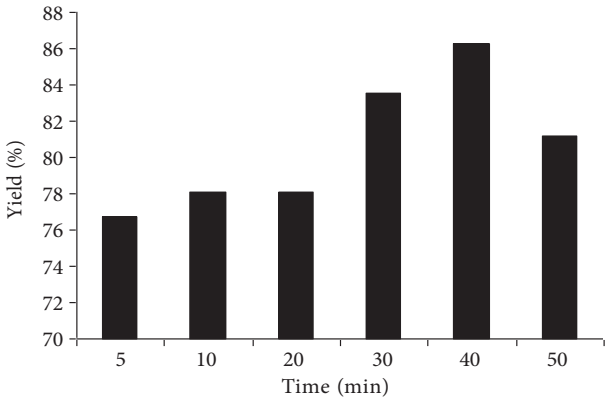


Figure 2. Effect of time on the yield of compound **3**.

To optimize the reaction MWI power, the reaction of hydrazide **3** with benzaldehyde was carried out at 100 W, 200 W, 300 W, 400 W, and 500 W for 2 min in the synthesis of **4a**. The results showed that the effect of MWI power on the yield of product **4a** is not large, but the yield of product **4a** slightly decreased as the MWI power increased. Therefore, 100 W was used for all the synthesizing of the other compounds (Figure 3).

Hydrazide **3** was then reacted with a series of commercially available aldehydes under both MWI and classical heating conditions to give the desired compounds **4a**–**p**. Compared with the 2–5-h reaction time using conventional heating, the reaction was carried out in a very short reaction time using the MWI. Nearly the same or higher product yields were obtained under MWI (Table). The results showed that MWI represented several advantages over classical heating. The melting points, molecular formulae, and weights of the synthesized compounds are also given in the Table.

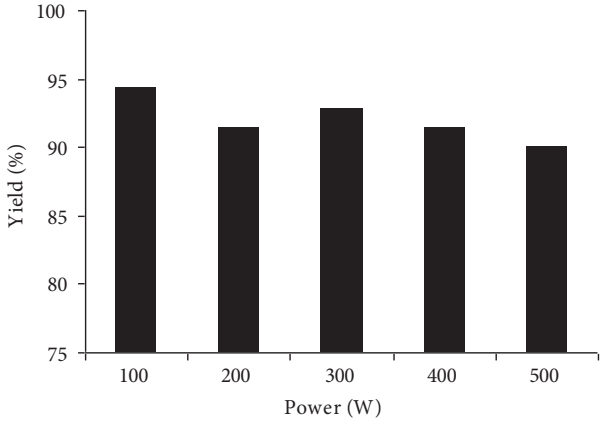


Figure 3. Effect of MWI power on the yield of compound **4**a.

Table. Molecular formula, molecular weight, melting points, reaction yields, and formulae of the compounds synthesized.

Entry	R	Molecular formula	Molecular weight (g/mol)	Time (min)		Yield (%)		Melting point (°C)
				CH	MW	CH	MW	
4a	H	$C_{20}H_{24}N_2O$	308.42	300[a]	4	87[a]	94	148.2–149.0
4b	2-Cl	$C_{20}H_{23}ClN_2O$	342.86	360[a]	2	79[a]	91	129.6–130.5
4c	3-Cl	$C_{20}H_{23}ClN_2O$	342.86	180	4	78	90	144.5–145.7
4d	4-Cl	$C_{20}H_{23}ClN_2O$	342.86	300[a]	2	77[a]	89	168.8–170.0
4e	2-Br	$C_{20}H_{23}BrN_2O$	387.31	120	2	86	92	137.2–138.0
4f	3-Br	$C_{20}H_{23}BrN_2O$	387.31	120	2	89	95	157.0–158.0
4g	4-Br	$C_{20}H_{23}BrN_2O$	387.31	60	2	82	88	171.0–173.0
4h	2-F	$C_{20}H_{23}FN_2O$	326.41	120	2	80	91	159.0–160.0
4i	3-F	$C_{20}H_{23}FN_2O$	326.41	180	2	93	94	130.5–132.0
4j	4-F	$C_{20}H_{23}FN_2O$	326.41	180	2	74	93	139.1–141.0
4k	2-OCH_3	$C_{21}H_{26}N_2O_2$	338.44	120	4	78	91	136.3–137.1
4l	3-OCH_3	$C_{21}H_{26}N_2O_2$	338.44	120	2	81	90	115.9–142.7
4m	4-OCH_3	$C_{21}H_{26}N_2O_2$	338.44	300[a]	4	85[a]	87	142.7–144.1
4n	2-CH_3	$C_{21}H_{26}N_2O$	322.44	120	2	86	92	147.5–148.6
4o	3-CH_3	$C_{21}H_{26}N_2O$	322.44	120	2	78	96	128.5–129.5
4p	4-CH_3	$C_{21}H_{26}N_2O$	322.44	120	2	92	96	152.2–152.8

[a]These data are taken from the literature.[24]

All unknown compounds were characterized by their melting points, IR, ^{1}H NMR, and APT-NMR spectra. The spectral data are in agreement with the literature and the proposed structures.[24]

From the spectroscopic studies, the infrared spectra of compound **3** showed absorption bands due to the stretching vibration of C = O and C-N at 1667 cm^{-1} and 1604 cm^{-1} and the spectra of compounds **4a**–**p** showed absorption bands of N-H, C = O, and C = N at 3210–3172 cm^{-1}, 1678–1650 cm^{-1}, and 1614–1596 cm^{-1}, respectively.

In the ^{1}H NMR spectra of each compound **3**, the amine protons were exhibited at δ 4.18 ppm and the amide proton was exhibited at δ 9.15 ppm as a singlet. All protons are in agreement with the literature data.[24]

In the ^{1}H NMR spectra of compounds **4a**–**p**, all groups exhibited 2 sets of signals. It is known that N-acylhydrazones can exist in 4 possible forms, as geometrical isomers (E/Z) in respect to C = N double bonds

and as rotamers (cis/trans) about amide N-C(O).[26–28] However, Palla et al. showed that the Z_{N-N} conformer is not realized because of steric hindrance even in hydrazones of aldehydes. Therefore, they claimed that N-acylhydrazones derived from aromatic aldehydes in solution are in the E form.[26] Syakaev et al. confirmed this result with X-ray data.[29]

Based on the literature data, the double signals in the NMR spectra of acylhydrazones **4a–p** can be attributed to the existence of amide conformers only. The signals belonging to the methylidene proton of one form was exhibited at δ 8.13–8.59 ppm, whereas the methylidene proton of the other form appeared at δ 7.86–8.31 ppm as a singlet. The amide proton of one form also appeared at δ 11.25–11.76 ppm, whereas the amide proton of the other form appeared at δ 11.11–11.48 ppm as a singlet. The other protons were observed according to the expected chemical shift and integral values.

The APT-NMR spectra of compound **3** showed the characteristic amide C = O carbon at approximately 174.2. All carbons peaks are in agreement with the literature data.[24]

In the APT-NMR spectra of compound **4a–p**, the chemical shift of amidic carbonyl groups of one form was exhibited at δ 169.7–170.5 ppm. The chemical shift of amidic carbonyl groups of the other form was exhibited at δ 175.0–175.7 ppm. The other carbons were observed according to the expected chemical shifts.

In conclusion, the author has developed a simple and efficient method for the synthesis of ibuprofen-based acylhydrazones. This method produces these products in good yields, with a short reaction time and easy workup. The isolated products are very pure and do not need any column purification. This study opens up a new area of cost-effective synthesis of potentially biologically active ibuprofen-based acylhydrazone compounds.

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