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Microwave synthesis of some new antimicrobial and antiproliferative butenamides and pyrrolidine-2,5-diones

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Microwave irradiation, comparable to conventional thermal heating, proves to be a convenient method in assisting the synthesis of some butenamides, pyrrolidine-2,5-diones, and their benzenesulfonamido derivatives, which are known to have biological activities and wide medical and industrial applications. Both procedures were used to compare their efficiency in synthesizing butenamides and pyrrolidine-2,5-diones (**2-25**), which have important and wide applications, from condensation of α,β-unsaturated anhydride (**1**) with the corresponding amines. Some of the products showed biological or cytotoxic (antiproliferative) activity.

Key Words: Microwave, butenamides, pyrrolidines, sulfonamides, biological activity, antiproliferative activity

Introduction

In the past few years, there has been exponentially growing attention paid to the use of microwave irradiation in organic synthesis. It proves to be a convenient method of heating, comparable to conventional thermal techniques, since it is clean and cheap and often results in higher yields with a shorter reaction time. Moreover, some reactions that do not take place by conventional thermal heating techniques or give low yields can be accomplished in high yields with microwave irradiation techniques. It is becoming an increasingly popular method of heating in industry, pharmaceutical applications, and academia.[1−6] The microwave irradiation of 3-carboxy-4-aryl-3-butenoic acid, 2-arylmethylenebutanedioic anhydride, and methyl 3-carboxy-4-aryl-3-butenoate with different hydrazines or aliphatic or aromatic amines gave 1,2-bis substituted hydrazines, hydrazides, butenamides,

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and/or butanimides in excellent yields and high purity in a short amount of time. Comparison with the conventional heating method showed that microwave heating is more convenient and promising.[7] The rapid synthesis of N-aryl imides from homophthalic anhydride or (4-methoxyphenyl)-5H-pyran-2,6-dione and aromatic amines under microwave irradiation using natural alumina as solid support in dry reaction conditions resulted in the increased purity of the products in shorter reaction times.[8] Microwave synthesis of imides from dicarboxylic acids with different amines, in one-pot reactions and in the absence of solvents, has been reported.[9] The conventional thermal condensation of γ-phenylitaconic anhydrides with hydrazine hydrate or aromatic or aliphatic amines gave the corresponding γ-aryl itaconic hydrazide, γ-aryl itaconamic acid, and γ-aryl itaconimide, respectively. The importance of the synthesized compounds was due to their biological activities.[10] The aim of the present work was to synthesize some new antimicrobial and antiproliferative butenamides and pyrrolidine-2,5-diones with high yield and purity in a short amount of time, and also to compare the microwave irradiation technique with conventional thermal heating.

Experimental

General remarks

Microwave irradiation was carried out in a Galanz microwave oven (WP1000AP30-2) at the Chemistry Department of the University College of Women for Arts, Science, and Education of Ain Shams University. Spectral measurements were carried out at the Micro Analytical Center, Faculty of Science of Cairo University, using:

(a) FTIR: PerkinElmer 1430 Infrared Spectrophotometer.

(b) MS spectra: GCMS QP 1000 EX Shimadzu.

(c) ^{1}H-NMR spectra: Varian Gemini (200 MHz).

(d) Biological activity: Antimicrobial screening was performed in the Botany Department of the University College of Women for Arts, Science, and Education of Ain Shams University, Asma Fahmy Street, Heliopolis, Cairo, Egypt.

(e) Antiproliferative activity measurements were carried out at the National Institute of Cancer of Cairo University, Cairo, Egypt.

General solvent-free microwave irradiation technique

In an open vessel, a homogenous, ground mixture of 2-diphenylmethylenebutanedioic anhydride (**1**)[11] with N-substituted 4-aminobenzenesulfonamides[12] **a-g** or amines **h-m** was dry irradiated for 2-5 min in a microwave oven (1000 W, 100% power). The reaction progress was monitored by thin layer chromatography (TLC) until no more unreacted materials were observed. The reaction mixture was then cooled to room temperature and dissolved in chloroform. The chloroform layer was washed with diluted HCl to get rid of unreacted amines, and then extracted with a 10% ice-cold sodium carbonate solution. Acidification of the aqueous layer with ice-cold concentrated hydrochloric acid precipitated the carboxylic compounds, N-(N′-substituted benzenesulfonamido)-3-carboxy-4-aryl-3-butenamide derivatives. Thorough washing of the organic layer with

water was followed by drying over anhydrous sodium sulfate and organic solvent distillation, which gave N-(N′-substituted benzenesulfonamido)-3-substituted pyrrolidine-2,5-dione derivatives. The products obtained were crystallized from ethanol.

General conventional thermal heating technique

A homogenous mixture of α,β-unsaturated anhydride (**1**)[11] with N-substituted 4-aminobenzenesulfonamides[12] **a-g** (1:2) and amines **h-m** was heated under reflux for at least 4 h in ethanol. The reaction progress was monitored by TLC. The reaction mixture was then concentrated; the precipitate formed was filtered and dissolved in chloroform and then worked up in the same way as described for the solvent-free microwave irradiation technique. Structures of the products were confirmed by spectral analyses, FTIR, ^{1}H-NMR, and MS.

Biological activity: Antimicrobial screening

The antimicrobial screening of the N-[N′-(4-substituted phenyl)benzenesulfonamido]-3-carboxy-4,4-diphenyl-3-butenamides and N-[N′-(4-substituted phenyl)benzenesulfonamido]-3-diphenylmethylenepyrrolidine-2,5-diones, using the disk diffusion method and inhibition zone diameter (mm/1 cm sample) in DMSO as a solvent, showed that all derivatives were highly active toward gram-positive and gram-negative bacteria, *Staphylococcus aureus* and *Escherichia coli*, respectively. Some compounds were also highly active toward fungi *Aspergillus flavus* and *Candida albicans*.

Butenamides showed higher biological activity than their corresponding pyrrolidine-2,5-diones. This can be ascribed to the presence of the carboxyl group. Moreover, compounds containing the electron-withdrawing chlorine atom or a nitro group showed higher biological activities than the others.

Medicinal application: Antiproliferative activity

Cytotoxic activity compounds **2**, **3**, **16**, and **24**, and 5-fluorouracil (5-fluoro-1H-pyrimidine-2,4-dione) as a reference drug, were tested against human breast carcinoma cell line MCF-7. The method applied was similar to that reported by Skehan et al.[13] The results obtained showed that compounds **2**, **3**, and **16** had low activity (3.68, 4.86, and 3.12 μg/mL IC50, respectively), whereas compound **24** was the most active (2.98 μg/mL IC50) compared to reference drug 5-fluorouracil (0.67 μg/mL IC50), where IC50 is defined as the concentration that results in a 50% decrease in cell number as compared with that of the control structures in the absence of an inhibitor.

N-(N′-Phenylbenzenesulfonamido)-3-carboxy-4,4-diphenyl-3-butenamide (2): White crystals, mp 142 °C, 0% yield in microwave and 14% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3394-3256 (2NH), 3400-2400 (OH, acid), 1702 (CO, acid), 1688 (CO, amide), and 1340 and 1156 (SO_2, asy. and sym.). MS: m/z = 512 (M^+, 0%, $C_{29}H_{24}N_2O_5S$), 495 (82.4, $C_{29}H_{23}N_2O_4S$), 494 (100, $C_{29}H_{22}N_2O_4S$), 339 (21.5, $C_{23}H_{17}NO_2$), 338 (83.1, $C_{23}H_{16}NO_2$), 219 (12.9, $C_{16}H_{11}O$), 193 (8.3, $C_{15}H_{13}$), 191 (71.8, $C_{15}H_{11}$), 156 (13.2, $C_6H_6NO_2S$), 115 (11.3, C_9H_7), and 92 (32.8, C_6H_6N).

N-(N′-Phenylbenzenesulfonamido)-3-diphenylmethylenepyrrolidine-2,5-dione (3): Pale yellow crystals, mp 251 °C, 71% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3189.3

(NH), 1774-1699 (2CO, imide), and 1379 and 1161 (SO_2, asy. and sym.). MS: m/z = 494 (M^+, 100%, $C_{29}H_{22}N_2O_4S$), 402 (24.2, $C_{23}H_{16}NO_4S$), 339 (29.2, $C_{23}H_{17}NO_2$), 338 (95.9, $C_{23}H_{16}NO_2$), 310 (42.6, $C_{22}H_{16}NO$), 232 (8, $C_{12}H_{10}NO_2S$), 220 (14.9, $C_{16}H_{12}O$), 219 (18.8, $C_{16}H_{11}O$), 191 (77.7, $C_{15}H_{11}$), 115 (16.4, C_9H_7), and 92 (49.8, C_6H_7N). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.06-7.53 (10H, m, $2C_6\underline{H}_5$), 3.62 (2H, s, $C\underline{H}_2$), 7.85-7.89 (2H, d, $\underline{Ph}SO_2$), 7.49-7.53 (2H, d, $\underline{Ph}NCO$), 10.42 (1H, s, $SO_2N\underline{H}$), and 7.32 (5H, s, $C_6\underline{H}_5$).

N-[N′-(4-Methylphenyl)benzenesulfonamido]-3-carboxy-4,4-diphenyl-3-butenamide (4): White crystals, mp 121 °C, 0% yield in microwave and 22% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3350-3250 (2NH), 3400-2400 (OH, acid), 1700 (CO, acid), 1686.3 (CO, amide), and 1329 and 1155 (SO_2, asy. and sym.). MS: m/z = 526 (M^+, 0%, $C_{30}H_{26}N_2O_5S$), 509 (39.4, $C_{30}H_{25}N_2O_4S$), 508 (53.1, $C_{30}H_{24}N_2O_4S$), 339 (46.9, $C_{23}H_{17}NO_2$), 338 (40.4, $C_{23}H_{16}NO_2$), 191 (49.6, $C_{15}H_{11}$), 107 (12.2, C_7H_9N), 106 (100, C_7H_8N), 92 (7, C_7H_8), and 91 (4.5, C_7H_7). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.28-7.34 (10H, m, $2C_6\underline{H}_5$), 3.20-3.80 (2H, imp., $C\underline{H}_2$), 10.37 (1H, s, $NHSO_2$), 7.66 (4H, s, $NHC_6\underline{H}_4SO_2$), 9.68 (1H, s, NHCO), 7.12-7.34 (2H, d, $NH\underline{Ph}$), 6.98-7.01 (2H, d, $\underline{Ph}CH_3$), 2.18-2.19 (3H, s, CH_3), and 12.20-12.40 (1H, broad, COOH).

N-[N′-(4-Methylphenyl)benzenesulfonamido]-3-diphenylmethylenepyrrolidine-2,5-dione (5): Pale yellow crystals, mp 160 °C, 85% yield in microwave and 42% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3248.5 (NH), 1778-1709 (2CO, imide), and 1334 and 1159 (SO_2, asy. and sym.). MS: m/z = 508 (M^+, 73.3%, $C_{30}H_{24}N_2O_4S$), 339 (36.4, $C_{23}H_{17}NO_2$), 338 (30.4, $C_{23}H_{16}NO_2$), 310 (11.2, $C_{22}H_{16}NO$), 219 (8.6, $C_{16}H_{11}O$), 156 (2.3, $C_6H_6NO_2S$), 115 (7.4, C_9H_7), 106 (100, C_7H_8N), and 92 (2.6, C_6H_6N).

N-[N′-(4-Methoxyphenyl)benzenesulfonamido]-3-carboxy-4,4-diphenyl-3-butenamide (6): White crystals, mp 196 °C, 0% yield in microwave and 29% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3287-3235 (2NH), 3400-2400 (OH, acid), 1700 (CO, acid), 1671 (CO, amide), and 1331 and 1160 (SO_2, asy. and sym.). MS: m/z = 542 (M^+, 0%, $C_{30}H_{26}N_2O_6S$), 525 (9.1, $C_{30}H_{25}N_2O_5S$), 524 (23.7, $C_{30}H_{24}N_2O_5S$), 339 (7, $C_{23}H_{17}NO_2$), 338 (10.5, $C_{23}H_{16}NO_2$), 192 (11.3, $C_{15}H_{12}$), 191 (22.3, $C_{15}H_{11}$), 123 (10, C_6H_5NS), 122 (100, C_7H_8NO), and 115 (2.7, C_9H_7). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.92-7.38 (10H, m, $2C_6\underline{H}_5$), 3.44 (2H, s, CH_2), 10.37 (1H, s, $NHSO_2$), 7.67 (2H, d, $\underline{Ph}SO_2$), 7.59-7.63 (2H, d, $\underline{Ph}NCO$), 9.81 (1H, s, NHCO), 6.96-6.99 (2H, d, $NH\underline{Ph}$), 6.78-6.83 (2H, d, $\underline{Ph}OCH_3$), 3.67 (3H, s, OCH_3), and 12.2-12.4 (1H, broad, COOH).

N-[N′-(4-Methoxyphenyl)benzenesulfonamido]-3-diphenylmethylenepyrrolidine-2,5-dione (7): Pale brown crystals, mp 103 °C, 87% yield in microwave and 41% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3249 (NH), 1774-1710 (2CO, imide), and 1335 and 1159 (SO2, asy. and sym.). MS: m/z = 524 (M^+, 31.6%, $C_{30}H_{24}N_2O_5S$), 338 (4, $C_{23}H_{16}NO_2$), 310 (4, $C_{22}H_{16}NO$), 219 (2.3, $C_{16}H_{11}O$), 193 (1.6, $C_{15}H_{13}$), 192 (6, $C_{15}H_{12}$), 191 (14.6, $C_{15}H_{11}$), 123 (8.2, C_6H_5NS), 122 (100, C_7H_8NO), and 108 (2.1, C_7H_8O). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.10-7.52 (10H, m, $2C_6\underline{H}_5$), 3.39 (2H, s, CH_2), 7.47-7.52 (2H, d, $\underline{Ph}NCO$), 7.78-7.82 (2H, d, $\underline{Ph}SO_2$), 10.07 (1H, s, $NHSO_2$), 6.99-7.04 (2H, d, $NH\underline{Ph}$), 6.71-6.83 (2H, d, $CH_3O\underline{Ph}$), and 3.62 (3H, s, OCH_3).

N-[N′-(4-Chlorophenyl)benzenesulfonamido]-3-carboxy-4,4-diphenyl-3-butenamide (8): White crystals, mp 149 °C, 22% yield in microwave and 43% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3381-3235 (2NH), 3400-2400 (OH, acid), 1701.6 (CO, acid), 1678 (CO, amide), and 1327 and 1160 (SO_2, asy. and sym.). MS: m/z =546 (M^+, 0%, $C_{29}H_{23}N_2O_5SCl$), 528 (68.6, $C_{29}H_{21}N_2O_4SCl$), 402 (38.75, $C_{23}H_{16}NO_4S$), 339 (50.4, $C_{23}H_{17}NO_2$), 338 (100, $C_{23}H_{16}NO_2$), 219 (10.5, $C_{16}H_{11}O$), 192 (36.3, $C_{15}H_{12}$),

191 (52.3, $C_{15}H_{11}$), 310 (22.8, $C_{22}H_{16}NO$), and 127 (22.3, C_6H_6NCl).

N-[N′-(4-Chlorophenyl)benzenesulfonamido]-3-diphenylmethylenepyrrolidine-2,5-dione (9): Pale yellow crystals, mp 99 °C, 50% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3246.6 (NH), 1771-1709 (2CO, imide), and 1378 and 1161 (SO_2, asy. and sym.). MS: m/z = 528 (M^+, 100%, $C_{30}H_{24}N_2O_5S$), 402 (41.8, $C_{23}H_{16}NO_4S$), 339 (20.1, $C_{23}H_{17}NO_2$), 338 (97.3, $C_{23}H_{16}NO_2$), 310 (25.4, $C_{22}H_{16}NO$), 193 (5, $C_{15}H_{13}$), 192 (46, $C_{15}H_{12}$), 191 (61.3, $C_{15}H_{11}$), 126 (30.2, C_6H_5NCl), and 115 (16.2, C_9H_7).

N-[N′-(4-Nitrophenyl)benzenesulfonamido]-3-carboxy-4,4-diphenyl-3-butenamide (10): White crystals, mp 160 °C, 34% yield in microwave and 62% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3398-3203 (2NH), 3400-2400 (OH, acid), 1701.8 (CO, acid), 1686 (CO, amide), and 1353 and 1149 (SO_2, asy. and sym.). MS: m/z = 557 (M^+, 0%, $C_{29}H_{23}N_3O_7S$), 402 (41.5, $C_{23}H_{16}NO_4S$), 338 (80.8, $C_{23}H_{16}NO_2$), 191 (100, $C_{15}H_{11}$), 156 (33.7, $C_6H_6NO_2S$), 122 (18.1, C_6H_4NO), 115 (17.6, C_9H_7), and 92 (31.6, C_6H_6N).

N-[N′-(4-Nitrophenyl)benzenesulfonamido]-3-diphenylmethylenepyrrolidine-2,5-dione (11): Brown crystals, mp 111 °C, 46% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3247 (NH), 1770-1712 (2CO, imide), and 1348 and 1128 (SO_2, asy. and sym.). MS: m/z = 539 (M^+, 2.4%, $C_{29}H_{21}N_3O_6S$), 402 (1.5, $C_{23}H_{16}NO_4S$), 339 (2.4, $C_{23}H_{17}NO_2$), 219 (2.4, $C_{16}H_{11}O$), 292 (1.5, $C_{12}H_{10}NO_4S$), 193 (0.6, $C_{15}H_{13}$), 143 (17.3, $C_{10}H_7O$), 142 (100, $C_{10}H_6O$), 138 (2.4, $C_6H_6N_2O_2$), and 115 (70, C_9H_7).

N-[N′-(1-Naphthyl)benzenesulfonamido]-3-carboxy-4,4-diphenyl-3-butenamide (12): White crystals, mp 160 °C, 66% yield in microwave and 66% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3396-3249.6 (2NH), 3400-2400 (OH, acid), 1701.5 (CO, acid), 1680 (CO, amide), and 1399 and 1156 (SO_2, asy. and sym.). MS: m/z = 562 (M^+, 0%, $C_{33}H_{26}N_2O_5S$), 545 (48.5, $C_{33}H_{25}N_2O_4S$), 544 (28.9, $C_{33}H_{24}N_2O_4S$), 338 (10, $C_{23}H_{16}NO_2$), 298 (11.8, $C_{16}H_{14}N_2O_2S$), 219 (11.5, $C_{16}H_{11}O$), 193 (2.6, $C_{15}H_{13}$), 192 (24, $C_{15}H_{12}$), 191 (27.3, $C_{15}H_{11}$), 142 (79.9, $C_{10}H_9N$), and 115 (100, C_9H_7).

N-[N′-(1-Naphthyl)benzenesulfonamido]-3-diphenylmethylenepyrrolidine-2,5-dione (13): Violet crystals, mp 92 °C, 19% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3241 (NH), 1766-1705.7 (2CO, imide), and 1301 and 1150 (SO_2, asy. and sym.). MS: m/z = 544 (M^+, 13.8%, $C_{23}H_{24}N_2O_4S$), 390 (1.8, $C_{32}H_{25}N_2O_3S$), 389 (4.2, $C_{32}H_{24}N_2O_3S$), 193 (2.1, $C_{15}H_{13}$), 192 (10.6, $C_{15}H_{12}$), 191 (8, $C_{15}H_{11}$), 156 (25.9, $C_6H_6NO_2S$), 142 (70.2, $C_{10}H_8N$), 115 (100, C_9H_7), and 92 (24, C_6H_6N).

N-(N′-Benzylbenzenesulfonamido)-3-carboxy-4,4-diphenyl-3-butenamide (14): White crystals, mp 130 °C, 92% yield in microwave and 62% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3316-3250 (2NH), 3400-2400 (OH, acid), 1700 (CO, acid), 1686 (CO, amide), and 1321 and 1154 (SO_2, asy. and sym.). MS: m/z = 526 (M^+, 0%, $C_{30}H_{26}N_2O_5S$), 264 (49.4, $C_{17}H_{14}NO_2$), 262 (35.2, $C_{13}H_{14}N_2O_2S$), 508 (29.2, $C_{30}H_{24}N_2O_4S$), 192 (73.8, $C_{15}H_{12}$), 191 (60.5, $C_{15}H_{11}$), 156 (21.4, $C_6H_6NO_2S$), 115 (10.8, C_9H_7), 106 (69.6, C_7H_8N), 93 (100, CH_3NO_2S), and 91 (45.2, C_7H_7). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.16-7.40 (10H, m, 2 C_6H_5), 3.46 (2H, s, CH_2CO), 10.39 (1H, s, NHCO), 7.76 (4H, s, $NHC_6\underline{H}_4SO_2$), 8.01-8.08 (1H, t, $N\underline{H}CH_2$), 3.94-3.97 (2H, d, $C\underline{H}_2NH$), 7.29 (5H, s, $CH_2C_6\underline{H}_5$), and 12.2-12.40 (1H, broad, COOH).

N-(4-Methylphenyl)-3-carboxy-4,4-diphenyl-3-butenamide (15): Pale yellow crystals, mp 191 °C, 0% yield in microwave and 71% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400 (NH, amide), 3400-2400 (OH, acid), 1710 (CO, acid), and 1640 (CO, amide). MS: m/z = 371 (M^+, 2.6%, $C_{24}H_{21}NO_3$), 353 (2.8,

$C_{24}H_{19}NO_2$), 264 (3.8, $C_{17}H_{12}O_3$), 192 (20.5, $C_{15}H_{12}$), and 107 (100, C_7H_9N). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.20-7.40 (10H, m, $2C_6H_5$), 3.28 (2H, imp., CH_2), 7.41-7.43 (2H, d, NHPh), 6.96-6.99 (2H, d, CH_3Ph), 2.19 (3H, s, CH_3), and 9.33 (1H, s, CONHPh).

N-(4-Methylphenyl)-3-diphenylmethylenepyrrolidine-2,5-dione (16): White crystals, mp 172 °C, 95% yield in microwave and 15% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1760-1703 (2CO, imide). MS: m/z = 353 (M^+, 44%, $C_{24}H_{19}NO_2$), 192 (100, $C_{15}H_{12}$), 191 (58, $C_{15}H_{11}$), and 115 (11, C_9H_7). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.20-7.40 (10H, m, $2C_6H_5$), 3.59 (2H, s, CH_2), 7.45-7.46 (2H, d, CONPh), 7.14-7.15 (2H, d, CH_3Ph), and 2.33 (3H, s, CH_3).

N-(4-Methoxyphenyl)-3-carboxy-4,4-diphenyl-3-butenamide (17): Gray crystals, mp 156 °C, 0% yield in microwave and 41% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3350 (NH, amide), 3400-2500 (OH, acid), 1700 (CO, acid), and 1640 (CO, amide). MS: m/z = 387 (M^+, 15%, $C_{24}H_{21}NO_4$), 369 (26, $C_{24}H_{19}NO_3$), 264 (9, $C_{17}H_{12}O_3$), 192 (58, $C_{15}H_{12}$), and 123 (100, C_7H_9NO). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.14-7.39 (10H, m, $2C_6H_5$), 3.59 (2H, s, CH_2), 6.60-6.63 (2H, d, NHPh), 6.48-6.51 (2H, d, CH_3OPh), 3.66 (3H, s, OCH_3), and 9.27 (1H, s, CONHPh).

N-(4-Methoxyphenyl)-3-diphenylmethylenepyrrolidine-2,5-dione (18): Dark gray crystals, mp 192 °C, 97% yield in microwave and 14% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1760-1703 (2CO, imide). MS: m/z = 369 (M^+, 66%, $C_{24}H_{19}NO_3$), 192 (100, $C_{15}H_{12}$), 191 (76, $C_{15}H_{11}$), and 115 (13, C_9H_7). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.19-7.42 (10H, m, $2C_6H_5$), 3.55 (2H, s, CH_2), 7.17-7.18 (2H, d, CONHPh), 6.97-6.98 (2H, d, CH_3OPh), and 3.76 (3H, s, OCH_3).

N-(4-Chlorophenyl)-3-carboxy-4,4-diphenyl-3-butenamide (19): Gray crystals, mp 196 °C, 0% yield in microwave and 88% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3350 (NH, amide), 3400-2500 (OH, acid), 1700 (CO, acid), and 1640 (CO, amide). MS: m/z = 391 (M^+, 2%, $C_{23}H_{18}NO_3Cl$), 373 (3, $C_{23}H_{16}NO_2Cl$), 264 (23, $C_{17}H_{12}O_3$), 192 (100, $C_{15}H_{12}$), 127 (91, C_6H_6NCl), and 111 (3, C_6H_4Cl).

N-(4-Chlorophenyl)-3-diphenylmethylenepyrrolidine-2,5-dione (20): Pale brown crystals, mp 150 °C, 93% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1758.6-1703 (2CO, imide). MS: m/z = 373 (M^+, 2.1%, $C_{23}H_{16}NO_2Cl$), 375 (M^{+2}, 1.3%), 262 (3.4, $C_{17}H_{12}NO_2$), 192 (4.1, $C_{15}H_{12}$), 130 (100, C_9H_6O), 129 (80, C_9H_5O), 127 (16.1, C_6H_6NCl), 153 (0.5, C_7H_4NOCl), 115 (67.1, C_9H_7), and 111 (1.6, C_6H_4Cl). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.54-7.58 (10H, m, $2C_6H_5$), 3.61 (2H, s, CH_2), 7.24-7.32 (2H, d, ClPh), and 7.36-7.42 (2H, d, CONPh).

N-(4-Nitrophenyl)-3-carboxy-4,4-diphenyl-3-butenamide (21): Yellow crystals, mp 190 °C, 0% yield in microwave and 69% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3319 (NH, amide), 3400-2500 (OH, acid), 1690 (CO, acid), and 1677 (CO, amide). MS: m/z = 402 (M^+, 0%, $C_{23}H_{18}N_2O_5$), 384 (6, $C_{23}H_{16}N_2O_4$), 264 (26, $C_{17}H_{12}O_3$), 191 (100, $C_{15}H_{11}$), 138 (53, $C_6H_6N_2O_2$), and 115 (46, C_9H_7).

N-(4-Nitrophenyl)-3-diphenylmethylenepyrrolidine-2,5-dione (22): Brown crystals, mp 186 °C, 92% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1770-1714 (2CO, imide). MS: m/z = 3843 (M^+, 28%, $C_{23}H_{16}N_2O_4$), 307 (10.3, $C_{17}H_{11}N_2O_4$), 231 (5.1, $C_{11}H_7N_2O_4$), 205 (6.4, $C_9H_5N_2O_4$), 192 (100, $C_{15}H_{12}$), 191 (59.3, $C_{15}H_{11}$), 164 (41, $C_7H_4N_2O_3$), and 115 (25.5, C_9H_7). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 7.33-7.43 (10H, m, $2C_6H_5$), 3.65 (2H, s, CH_2), 7.70-7.82 (2H, d, CONPh), and 8.25-8.335 (2H, d, NO_2Ph).

N-(1-Naphthyl)-3-carboxy-4,4-diphenyl-3-butenamide (23): Violet crystals, mp 212 °C, 17% yield in microwave and 44% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3249 (NH, amide), 3400-2500 (OH, acid), 1700 (CO, acid), and 1640 (CO, amide). MS: m/z = 407 (M^+, 0%, $C_{27}H_{21}NO_3$), 384 (3, $C_{27}H_{19}NO_2$), 264 (2, $C_{17}H_{12}O_3$), 192 (15, C_9H_8), 143 (100, $C_{10}H_9N$), and 115 (32, C_9H_7).

N-(1-Naphthyl)-3-diphenylmethylenepyrrolidine-2,5-dione (24): Pale brown crystals, mp 190 °C, 74% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1769-1711 (2CO, imide). MS: m/z = 389 (M^+, 12.9%, $C_{27}H_{19}NO_2$), 220 (2.2, $C_{16}H_{12}O$), 219 (4.3, $C_{16}H_{11}O$), 192 (14.3, $C_{15}H_{12}$), 191 (10.3, $C_{15}H_{11}$), 143 (27, $C_{10}H_9N$), 142 (100, $C_{10}H_8N$), 127 (6.5, $C_{10}H_7$), 115 (73.7, C_9H_7), 97 (1.8, $C_4H_3NO_2$), and 92 (5.4, C_6H_6N).

N-Benzyl-3-carboxy-4,4-diphenyl-3-butenamide (25): Pale blue crystals, mp 162 °C, 98% yield in microwave and 67% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3284 (NH, amide), 3400-2400 (OH, acid), 1680 (CO, acid), and 1640 (CO, amide). MS: m/z = 371 (M^+, 0%, $C_{24}H_{21}NO_3$), 353 (9, $C_{24}H_{19}NO_2$), 264 (7, $C_{17}H_{12}O_3$), 192 (37, $C_{15}H_{12}$), 115 (30, C_9H_7), and 91 (100, C_7H_7).

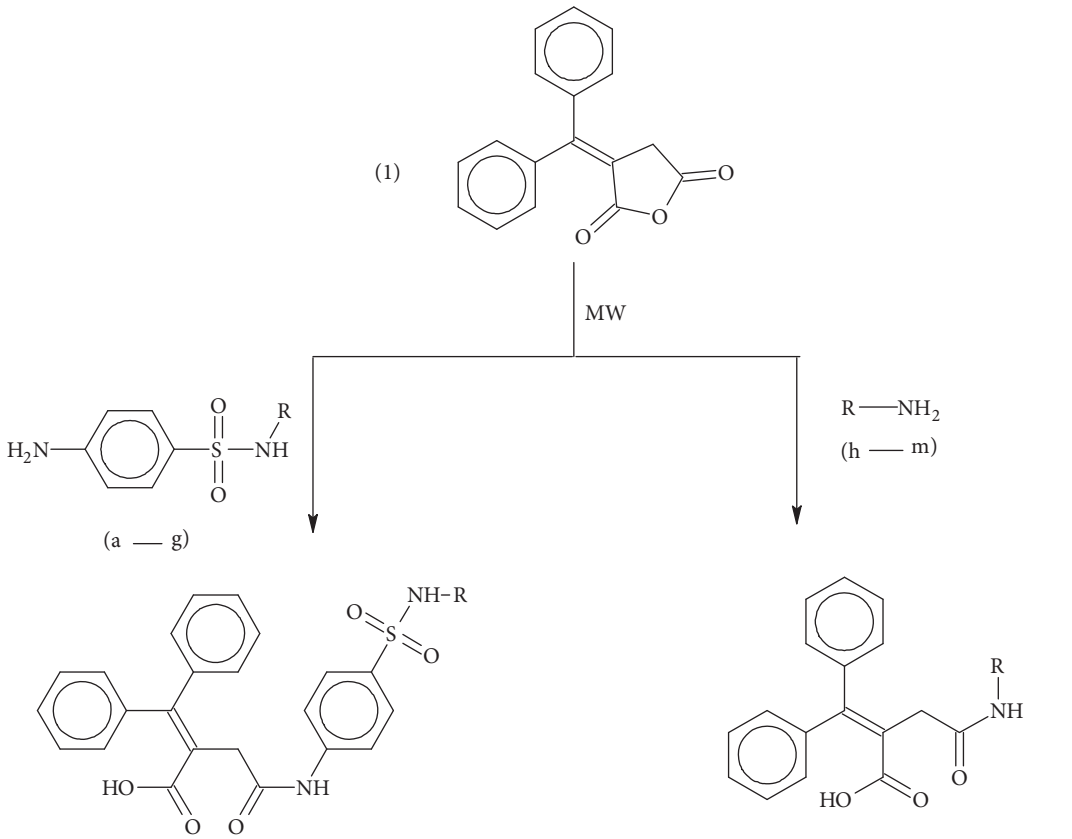
Results and discussion

Solvent-free microwave irradiation of anhydride (1) with N-substituted 4-aminobenzenesulfonamides (a-g) and amines (h-m)

Solvent-free microwave irradiation of 2-diphenylmethylenebutanedioic anhydride (**1**) with N-phenyl-4-aminobenzenesulfonamide (**a**), N-(4-methylphenyl)-4-aminobenzenesulfonamide (**b**), and N-(4-methoxyphenyl)-4-aminobenzenesulfonamide (**c**) gave pyrrolidine-2,5-diones **3**, **5**, and **7**, whereas with N-(4-chlorophenyl)-4-aminobenzenesulfonamide (**d**), N-(4-nitrophenyl)-4-aminobenzenesulfonamide (**e**), and N-(1-naphthyl)-4-aminobenzenesulfonamide (**f**), it gave separable mixtures from corresponding butenamides **8**, **10**, and **12** and pyrrolidine-2,5-diones **9**, **11**, and **13**. The formation of the separable mixtures can be ascribed to the low nucleophilicity of the amido nitrogen atom toward further intramolecular nucleophilic attack on the carbonyl carbon to give the corresponding pyrrolidine-2,5-diones.

However, reaction with N-benzyl-4-aminobenzenesulfonamide (**g**) gave butenamide **14** as the only product, which could be attributed to the steric effect exerted by the sp^3 tetrahedral carbon in the benzyl group in amine **g**, irrespective of the coplanarity of the 2 phenyl rings in anhydride **1**. The microwave irradiation of anhydride **1** with amines 4-methylaniline (**h**), 4-methoxyaniline (**i**), 4-chloroaniline (**j**), and 4-nitroaniline (**k**) gave corresponding pyrrolidine-2,5-diones **16**, **18**, **20**, and **22**, whereas with 1-naphthylamine (**l**) it gave a separable mixture from butenamide **23** and pyrrolidine-2,5-dione **24**, and with benzylamine (**m**) it gave butenamide **25** as the only product, due to the steric effect exerted by the sp^3 tetrahedral carbon in the benzyl group (Scheme 1).

In general, the results obtained from microwave irradiation of N-substituted 4-aminobenzenesulfonamides **a-g** with anhydride **1** show the low reactivity of the butenamides toward further cyclization, more so than with amines **h-m**. This can be attributed to the low basicity of amines **a-g** due to the presence of benzenesulfonamido moiety.



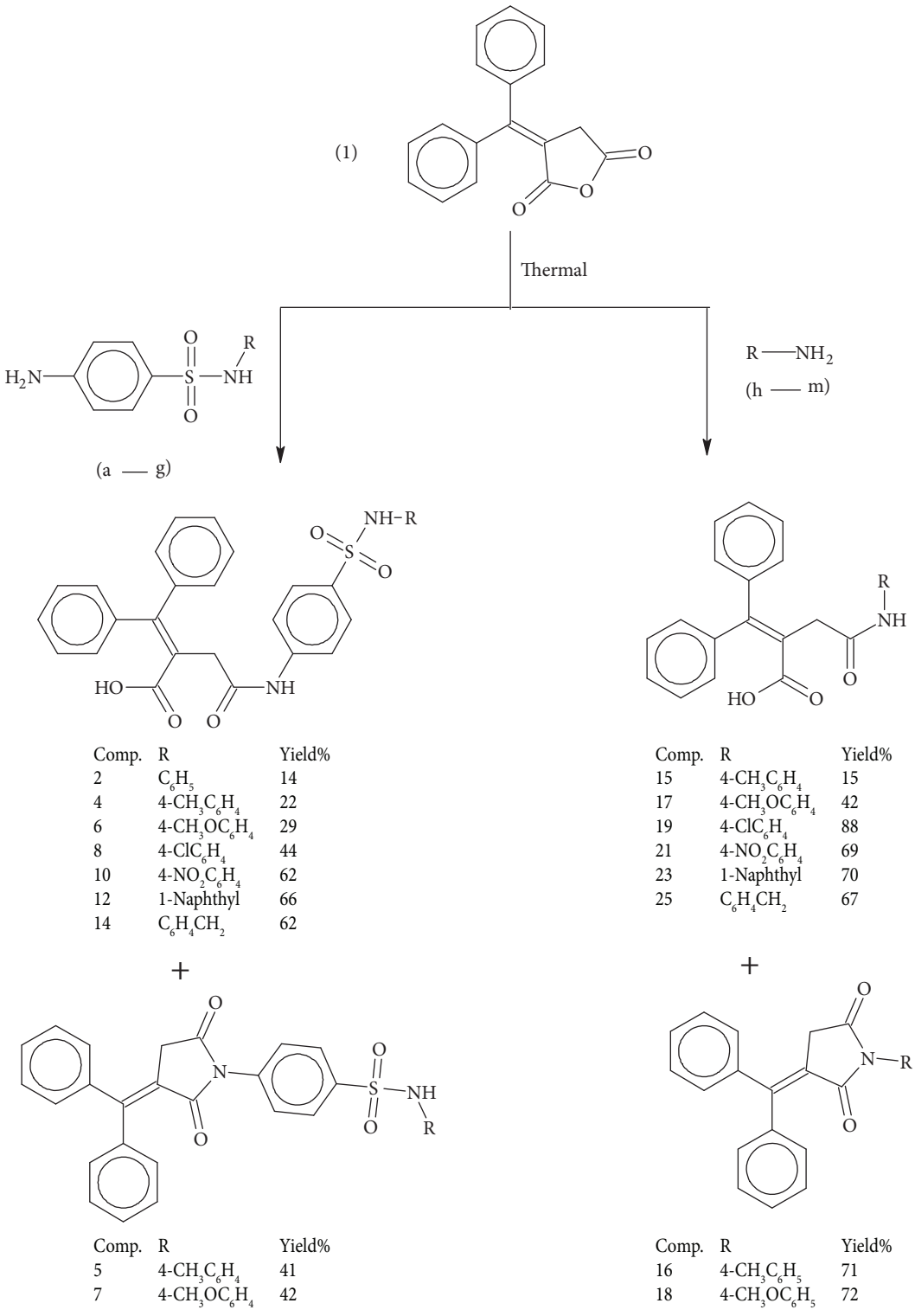
Comp.	R	Yield%
8	4-ClC_6H_4	27
10	4-$NO_2C_6H_4$	34
12	1-Naphthyl	66
14	$C_6H_4CH_2$	92

Comp.	R	Yield%
23	1-Naphthyl	12
25	$C_6H_4CH_2$	

Comp.	R	Yield%
3	C_6H_5	71
5	4-$CH_3C_6H_4$	84
7	4-$CH_3OC_6H_4$	96
9	4-ClC_6H_4	50
11	4-$NO_2C_6H_4$	46
13	1-Naphthyl	19

Comp.	R	Yield%
16	4-$CH_3C_6H_4$	95
18	4-$CH_3OC_6H_4$	97
20	4-ClC_6H_4	93
22	4-$NO_2C_6H_4$	92
24	1-Naphthyl	74

Scheme 1.



Comp.	R	Yield%
2	C_6H_5	14
4	4-$CH_3C_6H_4$	22
6	4-$CH_3OC_6H_4$	29
8	4-ClC_6H_4	44
10	4-$NO_2C_6H_4$	62
12	1-Naphthyl	66
14	$C_6H_4CH_2$	62

Comp.	R	Yield%
15	4-$CH_3C_6H_4$	15
17	4-$CH_3OC_6H_4$	42
19	4-ClC_6H_4	88
21	4-$NO_2C_6H_4$	69
23	1-Naphthyl	70
25	$C_6H_4CH_2$	67

Comp.	R	Yield%
5	4-$CH_3C_6H_4$	41
7	4-$CH_3OC_6H_4$	42

Comp.	R	Yield%
16	4-$CH_3C_6H_5$	71
18	4-$CH_3OC_6H_5$	72

Scheme 2.

Conventional thermal heating of anhydride (1) with N-substituted 4-aminobenzenesulfonamides (a-g) and amines (h-m)

The conventional thermal heating technique for anhydride **1** with amines **a** and **d-g** gave butenamides **2**, **8**, **10**, **12**, and **14** as the only products, whereas with amines **b** and **c**, it gave separable mixtures from corresponding butenamides **4** and **6** and pyrrolidine-2,5-diones **5** and **7**, respectively. The formation of the separable mixtures can be ascribed to the presence of the electron-donating methyl and methoxyl groups, which increase the basicity of the amido nitrogen atom toward nucleophilic attack on the carbonyl carbon.

Similarly, the condensation of anhydride **1** with amines **h** and **i** gave the corresponding separable mixtures from butenamides **15** and **17** and pyrrolidine-2,5-diones **16** and **18**, respectively, whereas with amines **j-m**, it gave corresponding butenamides **19**, **21**, **23**, and **25**, respectively, as the only products (Scheme 2).

Comparison between the yields obtained from condensation of anhydride **1** with amines **h** and **i** shows that amines **b** and **c** offered low yields due to the presence of benzenesulfonamido moiety (Table).

Table. Comparison of yields of products resulting from the microwave irradiation and conventional thermal heating techniques.

Amine	Product (Yield %)			
	Microwave heating		Conventional thermal heating	
	Butenamide	Pyrrolidine-2,5-dione	Butenamide	Pyrrolidine-2,5-dione
N-Phenyl-4-amino-benzenesulfonamide	-	3; 71%	2; 14%	-
N-(4-Methylphenyl)-4-aminobenzenesulfonamide	-	5; 84%	4; 22%	5; 41%
N-(4-Methoxyphenyl)-4-aminobenzenesulfonamide	-	7; 86%	6; 29%	7; 42%
N-(4-Chlorophenyl)-4-aminobenzenesulfonamide	8; 22%	9; 50%	8; 44%	-
N-(4-Nitrophenyl)-4-aminobenzenesulfonamide	10; 34%	11; 46%	10; 62%	-
N-(1-Naphthyl)-4-aminobenzenesulfonamide	12; 66%	13; 19%	12; 66%	-
N-Benzyl-4-aminobenzenesulfonamide	14; 92%	-	14; 62%	-
4-Methylaniline	-	16; 95%	15; 15%	16; 71%
4-Methoxyaniline	-	18; 97%	17; 42%	18; 72%
4-Chloroaniline	-	20; 93%	19; 88%	-
4-Nitroaniline	-	22; 92%	21; 69%	-
1-Naphthylamine	23; 17%	24; 74%	23; 70%	-
Benzylamine	25; 98%	-	25; 67%	-

In general, the butenamides that resulted from amines **j-m** were in better yields than those produced from amines **d-g** (Table).

Structural effect of α,β-unsaturated anhydride on the reactions

Comparison between the products obtained from both the microwave irradiation and conventional thermal heating of anhydride **1**, 2-methylphenylmthylenebutanedioic anhydride, or 2-phenylmethylenebutanedioic anhydride[14,15] with different N-substituted 4-aminobenzenesulfonamide derivatives (**a-g**) or amines (**h-m**) shows that the steric factor exerted by the presence of the sp^3 carbon of the methyl group in 2-methylphenylmethylenebutanedioic anhydride decreased its reactivity toward cyclization compared to the other 2 anhydrides. However, the coplanarity exerted by the 2 phenyl rings in anhydride **1** facilitated the further intramolecular nucleophilic attack of the amido nitrogen atom on the carbonyl carbon to give the corresponding pyrrolidine-2,5-diones.

Conclusion

In the present work, comparison showed that microwave irradiation accomplishes reactions with excellent yields and purity and in shorter times, assists cyclization, and shows regiospecific properties much more so than the conventional thermal heating technique. Furthermore, it proved to be more economical and environmentally friendly (green chemistry). Both microwave irradiation and conventional thermal heating techniques of N-substituted 4-aminobenzenesulfonamides with α,β-unsaturated anhydrides showed lower reactivity than the corresponding nonsulfonated amines, which could be attributed to the presence of the benzenesulfonamido group.

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