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Neat Reaction Technology for the Synthesis of 4-Oxo-thiazolidines Derived from 2-SH-Benzothiazole and Antimicrobial Screening of Some Synthesized 4-Thiazolidinones†

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†This paper is dedicated to Prof. K.R. Desai in recognition of his outstanding contributions to "Green Chemistry"

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The synthesis of 4-thiazolidinones **4a-j** in a good yields from the heterocyclization reaction of 2-(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide **3a-j** with $SHCH_2COOH$ in DMF in the presence of a catalytic amount of anhydrous $ZnCl_2$ under microwave irradiation is described and compared with conventional synthesis methods. All structures of the newly synthesized compounds were elucidated by elemental analysis and spectral data. Some of the new compounds were tested against bacteria (*Gram– ve* and *Gram+ ve*) and fungi.

Keywords: 4-Thiazolidinones, Heterocyclization, Microwave effect, Antimicrobial activity

INTRODUCTION

2-Mercaptobenzothiazole derivatives are known to possess various biological activities [1]. 4-Thiazolidinones are also well known for versatile pharmacological activities such as hypnotic [2], anaesthetic [3], antifungal [4], anthelmintic [5], and antiviral [6] agents, as well as CNS [7] stimulants. The incorporation of the 4-oxothiazolidine moiety into a 2-mercaptobenzothiazole scaffold enhances its activity [8]. The synthetic route of the abovementioned compounds is shown in Scheme 1.

In the last few years, microwave-induced organic reaction enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid synthesis [9] and many researchers have described accelerated organic reactions, with a large number of papers proving the synthetic utility of MORE chemistry in routine organic synthesis [10,11]. It can be termed "e-chemistry" because it is easy, effective, economical and eco-friendly and is believed to be a step toward green chemistry.

Under the framework of green chemistry [12-14], and following earlier reported applications of MORE [15-18] chemistry, we now report a novel, environmentally benign approach using a facile, $ZnCl_2$-mediated microwave synthesis of 4-thiazolidinones.

EXPERIMENTAL

Regents, Instrumentation and Measurements

All reagents, 2-mercaptobenzothiazole, solvents and catalyst were of analytical grade and used directly. All the melting points were determined using a PMP-DM scientific melting point apparatus and are uncorrected. The purity of compounds was checked routinely by thin layer

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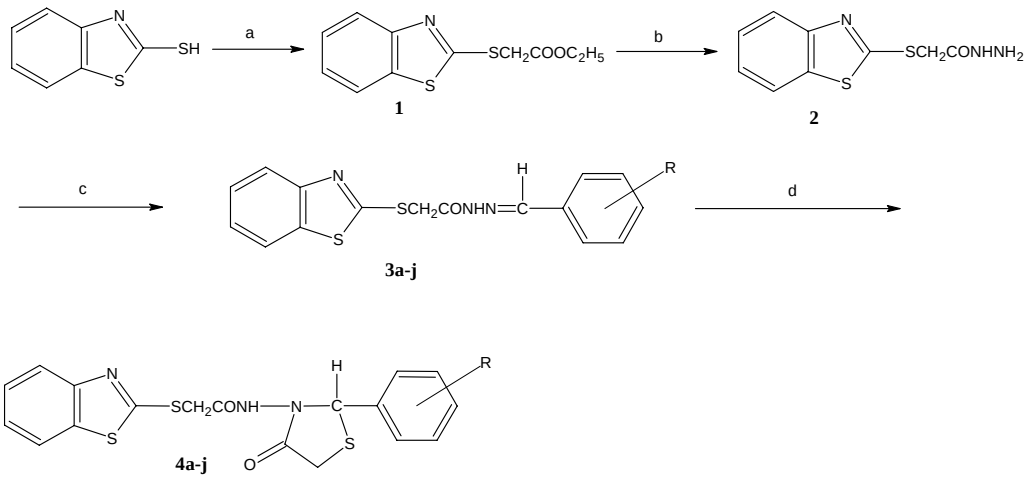

a) $ClCH_2COOC_2H_5$, anhydrous K_2CO_3, dry acetone; b) NH_2NH_2, ethanol; c) substituted aromatic aldehyde, 2-3 drops of gl. AcOH, ethanol; d) $SHCH_2COOH$, anhydrous $ZnCl_2$, DMF.

Scheme 1

chromatography (TLC) using silica gel-G coated Al-plates (0.5 mm thickness, Merck) and spots were visualized by exposing the dry plates to iodine vapor. IR spectra (υ_{max} in cm^{-1}) were recorded on a Shimadzu FT-IR 8300 spectrophotometer using KBr or the Nujol technique; ^1H NMR spectra were acquired on a Bruker WM 400FT 400 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal reference (chemical shifts in ppm); ^{13}C NMR was performed on a Varian AMX 400 (100 MHz) spectrometer using solutions in $CDCl_3$ and mass spectra were acquired on a Jeol JMS D-300 spectrometer operating at 75 eV. The elemental analysis (C, H, N) of compounds was performed on Carlo Erba-1108 elemental analyzer. Their results were found to be in good agreement with the calculated values. The microwave assisted reactions were carried out using a QPro-M Microwave Sample Preparation System (Questron Technologies Corporation, Mississauga, Ontario, Canada), wherein microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100 to 500 watts and an infrared sensor for temperature control with an attached reflux condenser with constant stirring (to avoid the risk of high pressure development). The QPro-M apparatus used, as shown in Fig. 1, was especially well-suited for stringent reaction conditions, including anhydrous atmosphere.

Microwave-mediated synthesis of ethyl 2-(benzothiazolylthio)acetate (1). Mercaptobenzothiazole (0.01 mol, 1.67 g) and ethylchloroacetate (0.01 mol, 1.22 ml) in dry acetone (4 ml) in the presence of anhydrous K_2CO_3 (1 g) were placed in a round bottom flask and microwave irradiated (300 W, 61-62 ^oC) for 4.0 min [21,22]. Upon completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature and the treated with cold water. The separated solid was filtered, washed with water and recrystallized from chloroform to furnish compound **1**, yield 76%, as a white crystal. m.p.: 58-59 ^oC. Anal.: Calcd. for $C_{11}H_{11}NO_2S_2$: C, 52.18; H, 4.22; N, 5.40. Found: C, 52.16; H, 4.23; N, 5.38%; IR: ν (cm^{-1}) 3023 (aromatic ring), 1070 (aliphatic ether), 638 (C-S), 1723 (>C=O of ester), 1614 (-C=N-), 1223 and 1041 (C-O-C), 721 (C-S-C) and 2915, 2871, 1423, 713 (-CH_2 and -CH_3); ^1H NMR: δ (ppm) 1.23 (t, 3H, J = 7 Hz, -$COOCH_2CH_3$), 4.13 (q, 2H, J = 7 Hz, -$COOCH_2CH_3$), 4.46 (s, 2H, S-CH_2-), 6.73-7.87 (m, 4H, Ar-H).

Conventional synthesis of ethyl 2-(benzothiazolylthio)acetate (1). An equimolar solution of 2-mercaptobenzothiazole (0.01 mol, 1.67 g) and ethyl chloroacetate (0.01 mol, 1.22 ml) in dry acetone (4 ml) in the presence of anhydrous K_2CO_3 (1 g) was refluxed on a water bath for 16 h. The solvent was removed by vacuum distillation and the residue was recrystallized from chloroform to furnish compound **1**, yield 66%, as a white solid. m.p.: 58-59 ^oC.

Microwave-mediated synthesis of 2-(benzothiazol-2-

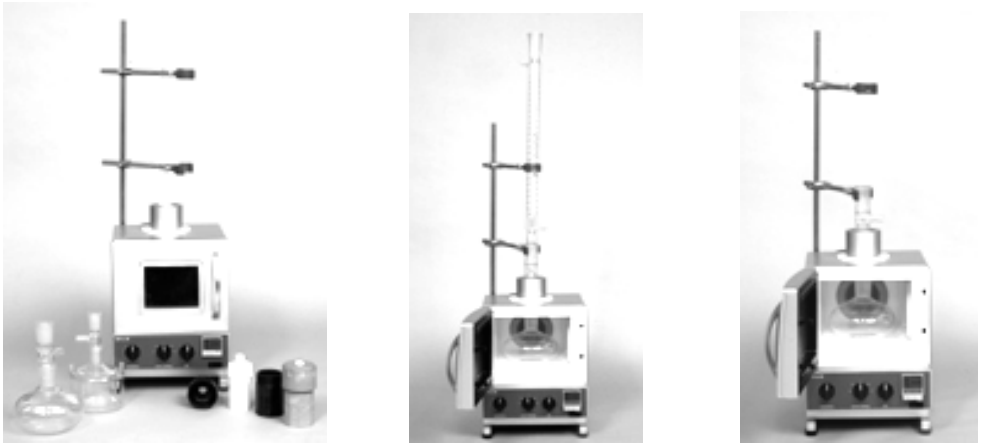

Fig. 1. QPro-M Microwave System.

ylthio)acetohydrazide (2). Compound **1** [23,24] (0.01 mol, 2.53 g) and hydrazine hydrate (0.01 mol, 0.9 ml) in ethanol (20 ml) were placed in a round bottom flask and microwave irradiated (350 W, 76-78 ^{o}C) for 3.5 min [21,22]. After completion of the reaction (monitored by TLC.), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol to give compound **2**, yield 78%, as a pinkish-white powder. m.p.: 192-193 ^{o}C. Anal.: Calcd. for $C_9H_9N_3OS_2$: C, 45.22; H, 3.10; N, 17.60. Found: C, 45.19; H, 3.07; N, 17.57%; IR: ν (cm^{-1}) 3352, 3378 (-$NHNH_2$), 1665 (>C=O of amide); ^{1}H NMR: δ (ppm) 6.80-7.90 (m, 4H, Ar-H), 4.40 (s, 2H, -NH_2), 4.81 (s, 2H, S-CH_2-), 7.88 (s, 1H, -CONH-).

Conventional synthesis of 2. Compound **1** (0.01 mol, 2.53 g) and hydrazine hydrate (0.01 mol, 0.9 ml) in ethanol (20 ml) were refluxed for about 5 h on a steam bath. After cooling the resulting solid was filtered, dried and recrystallized from ethanol to obtain compound **2**, yield 61%, as a pinkish-white solid. m.p.: 192-193 ^{o}C.

Microwave-mediated synthesis of 2-(benzothiazol-2-ylthio)-N'-4-nitrobenzylideneacetohydrazide (3a). A mixture of compound **2** [23,24] (0.01 mol, 2.39 g) and 4-nitrobenzaldehyde (0.01 mol, 1.51 g) and 2-3 drops of glacial acetic acid in ethanol (20 ml) were placed in a round bottom flask and microwave irradiated (400 W, 76-78 ^{o}C) for 3 min [21,22]. After completion of the reaction (monitored by TLC), the solvent was removed and residue recrystallized from the chloroform-methanol mixture to obtain compound **3**, yield 75%, as a pale yellow crystal. m.p.: 153-155 ^{o}C. Anal.: Calcd. for $C_{16}H_{12}N_4O_3S_2$: C, 51.50; H, 3.16; N, 14.91. Found: C, 51.47; H, 3.15; N, 14.87%; IR: ν (cm^{-1}) 3340, 1335 (-NH-), 1668 (>C=O), 1626 (-N=CH-); ^{1}H NMR: δ (ppm) 4.40 (s, 1H, -N=CH-), 8.13 (s, 1H, -CONH-), 6.93-7.73 (m, 4H, Ar-H).

Conventional synthesis of 3a. A mixture of compound **2** (0.01 mol, 2.39 g) and 4-nitrobenzaldehyde (0.01 mol, 1.51 g) and 2-3 drops of glacial acetic acid in ethanol (25 ml) was refluxed on a water bath for about 6 h. The solvent was removed and residue recrystallized from a chloroform-methanol mixture to yield compound **3a**, (59%) as a pale yellow powder. m.p.: 153-155 ^{o}C. Compounds **3b-j** were prepared similarly by treating **2** with various aromatic aldehydes.

Microwave mediated synthesis of 3-{[2-(benzothiazol-2-ylthio)ethyl]amino}-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (4a). A mixture of **3a** [23,24] (0.01 mol, 3.72 g) in DMF and thioglycollic acid (0.01 mol, 0.92 ml) with a pinch of $ZnCl_2$ were placed in a round bottom flask and microwave irradiated (400 W, 146 ^{o}C) for 3 min [21,22]. After completion of the reaction (monitored by TLC), the solution was then diluted with ice cold water. The solid product that formed was filtered, dried and recrystallized from ethanol, yield 86%, as a dark yellow solid.

Conventional synthesis of 4a. A mixture of **3a** (0.01 mol, 3.72 g) in ethanol and thioglycollic acid (0.01 mol, 0.92 ml) with a pinch of $ZnCl_2$ were placed in a round bottom flask and refluxed for 8 h on a steam bath. After completion of the reaction (monitored by TLC), the ethanol was distilled off to obtain product **4a**. The solid product was filtered, dried and recrystallized from ethanol, yield 68%, as a yellow powder. Compounds **4b-j** were prepared similarly, using **3b-j** respectively.

Spectral DATA of 4-Thiazolidinones (4a-j)

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (4a). Yellow powder, m.p.: 168 ºC; Anal.: Calcd. for $C_{18}H_{14}N_4O_4S_3$: C, 48.45; H, 3.15; N, 12.58. Found: C, 48.43; H, 3.13; N, 12.55%; IR: ν (cm^{-1}) 3340, 1330 (-NH-), 1665 (>C=O, amidyl), 1717 (>C=O, cyclic), 1340 (Ar-NO_2); ^{1}H NMR: δ (ppm) 8.53 (s, 1H, -CONH-), 7.00-7.95 (m, 8H, Ar-H), 3.15 (s, 1H, -N=CH-), 4.48 (s, 2H, S-CH_2-), 3.60 (s, 2H, -CH_2-thiazolidinone); ^{13}C NMR: δ (ppm) 127 (C_1), 128.9 (C_2, C_6), 126.2 (C_3, C_5), 150 (C_4), 60 (>$C_{2'}$H-N<), 30 (-S-CH_2-), 172.5 (cyclic, >$C_{4'}$=O), 169.2 (amide, >C=O), 57 (-CH_2-thiazolidinone), 157.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 446[M^+] ($C_{18}H_{14}O_4N_4S_3^+$), 238 ($C_9H_5O_3N_3S^+$), 223 ($C_9H_7O_3N_2S^+$), 210 ($C_8H_8O_2N_3S^+$), 208 ($C_9H_4ONS_2^+$), 195 ($C_8H_7O_2N_2S^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\,N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(3,4,5-trimethoxyphenyl)-1,3-thiazolidin-4-one (4b). White powder, m.p.: 240 ºC; Anal.: Calcd. for $C_{21}H_{20}N_3O_5S_3$: C, 51.36; H, 4.05; N, 8.51. Found: C, 51.32; H, 4.07; N, 8.55%; IR: ν (cm^{-1}) 3335, 1335 (-NH-), 1660 (>C=O, amidyl), 1720 (>C=O, cyclic), 2825 (Ar-OCH_3); ^{1}H NMR: δ (ppm) 8.50 (s, 1H, -CONH-), 6.98-7.93 (m, 8H, Ar-H), 3.18 (s, 1H, -N=CH-), 4.46 (s, 2H, S-CH_2-), 3.63 (s, 2H, -CH_2-thiazolidinone), 3.91 (s, 3H, -OCH_3); ^{13}C NMR: δ (ppm) 127.1 (C_1), 129.1 (C_2, C_6),126.4 (C_3, C_5), 153 (C_4), 52.3 (>$C_{2'}$H-N<), 30.1 (-S-CH_2-), 172 (cyclic, >$C_{4'}$=O), 168.2 (amide, >C=O), 58 (-CH_2-thiazolidinone), 156.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics), 35.4 ($CH_3OC_6H_4$-); MS (*m/z*): 491[M^+] ($C_{21}H_{20}N_3O_5S_3^+$), 283 ($C_{12}H_{16}O_4N_2S^+$), 268 ($C_{12}H_{15}O_4NS^+$), 255 ($C_{11}H_{16}O_3N_2S^+$), 240 ($C_{11}H_{16}O_3N_2S^+$), 208 ($C_9H_4ONS_2^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\,N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(2-hydroxyphenyl)-1,3-thiazolidin-4-one (4c). Yellow crystalline powder, m.p.: 131 ºC; Anal.: Calcd. for $C_{18}H_{15}N_3O_3S_3$: C, 51.81; H, 3.61; N, 10.05. Found: C, 51.79; H, 3.59; N, 10.07%. IR: ν (cm^{-1}): 3290, 1338 (-NH-), 1670 (>C=O, amidyl), 1725 (>C=O, cyclic), 3590 (Ar-OH); ^{1}H NMR: δ (ppm) 8.49 (s, 1H, -CONH-), 7.20-7.90 (m, 8H, Ar-H), 3.17 (s, 1H, -N=CH-), 4.31 (s, 2H, S-CH_2-), 3.61 (s, 2H, -CH_2-thiazolidinone), 3.65 (s, 1H, -OH); ^{13}C NMR: δ (ppm) 126.9 (C_1), 128.8 (C_2, C_6), 127 (C_3, C_5), 155 (C_4), 53.3 (>$C_{2'}$H-N<), 31.5 (-S-CH_2-), 175 (cyclic, >$C_{4'}$=O), 167.2 (amide, >C=O), 59 (-CH_2-thiazolidinone), 154.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 417[M^+] ($C_{18}H_{15}N_3O_3S_3^+$), 209 ($C_9H_{11}O_2N_2S^+$), 208 ($C_9H_4ONS_2^+$), 194 ($C_9H_{10}O_2NS^+$), 181 ($C_8H_{11}ON_2S^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\,N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(3-hydroxyphenyl)-1,3-thiazolidin-4-one (4d). Light yellow, m.p.: 143 ºC; Anal.: Calcd. for $C_{18}H_{15}N_3O_3S_3$: C, 51.82; H, 3.63; N, 10.11. Found: C, 51.80; H, 3.61; N, 10.10%. IR: ν (cm^{-1}) 3333, 1341 (-NH-), 1680 (>C=O, amidyl), 1734 (>C=O, cyclic), 3571 (Ar-OH); ^{1}H NMR: δ (ppm) 8.55 (s, 1H, -CONH-), 6.85-7.65 (m, 8H, Ar-H), 3.11 (s, 1H, -N=CH-), 4.36 (s, 2H, S-CH_2-), 3.59 (s, 2H, -CH_2-thiazolidinone), 3.64 (s, 1H, -OH); ^{13}C NMR: δ (ppm) 127.1 (C_1), 129.3 (C_2, C_6), 126.8 (C_3, C_5), 153.5 (C_4), 54.3 (>$C_{2'}$H-N<), 32.5 (-S-CH_2-), 175.2 (cyclic, >$C_{4'}$=O), 166.7 (amide, >C=O), 59.1 (-CH_2-thiazolidinone), 153.8 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 416[M^+] ($C_{18}H_{15}N_3O_3S_3^+$), 208 ($C_9H_4ONS_2^+$), 193 ($C_9H_{10}O_2NS^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 165 ($C_8H_{10}ONS^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\,N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one (4e). Brown crystal, m.p.: 159 ºC; Anal.: Calcd. for $C_{18}H_{15}N_3O_3S_3$: C, 51.80; H, 3.60; N, 10.03. Found: C, 51.77; H, 3.57; N, 10.05%; IR: ν (cm^{-1}) 3390, 1337 (-NH-), 1679 (>C=O, amidyl), 1730 (>C=O, cyclic), 3583 (Ar-OH); ^{1}H NMR: δ (ppm) 8.46 (s, 1H, -CONH-), 6.88-7.90 (m, 8H, Ar-H), 3.12 (s, 1H, -N=CH-), 4.45 (s, 2H, S-CH_2-), 3.62 (s, 2H, -CH_2-thiazolidinone), 3.58 (s, 1H, -OH); ^{13}C NMR: δ (ppm) 126.8 (C_1), 128.5 (C_2, C_6), 127.1 (C_3, C_5), 154 (C_4), 56 (>$C_{2'}$H-N<), 32 (-S-CH_2-), 176.2 (cyclic, >$C_{4'}$=O), 168.7 (amide, >C=O), 59.5 (-CH_2-thiazolidinone), 155.8 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 418[M^+] ($C_{18}H_{15}N_3O_3S_3^+$), 210 ($C_9H_{11}O_2N_2S^+$), 208 ($C_9H_4ONS_2^+$), 195 ($C_9H_{10}O_2NS^+$), 182 ($C_8H_{11}ON_2S^+$), 180 ($C_8H_4NS_2^+$), 167 ($C_8H_{10}ONS^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\,N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (4f). Dark yellow, m.p.: 188 ºC; Anal.: Calcd. for $C_{19}H_{17}N_3O_3S_3$: C, 52.92; H, 3.96; N, 9.10. Found: C, 52.90; H, 3.94; N, 9.07%; IR: ν (cm^{-1}): 3375, 1337 (-NH-), 1671 (>C=O, amidyl), 1726 (>C=O, cyclic), 2828 (Ar-OCH_3); ^{1}H NMR: δ (ppm) 8.47 (s, 1H, -CONH-), 6.88-7.95 (m, 8H, Ar-H), 3.13 (s, 1H, -N=CH-), 4.49 (s, 2H, S-CH_2-), 3.64 (s, 2H, -CH_2-

thiazolidinone), 3.96 (s, 3H, -OCH_3); ^{13}C NMR: δ (ppm) 126.8 (C_1), 128.7 (C_2, C_6), 125.9 (C_3, C_5), 153.2 (C_4), 53.1 (>$C_{2'}$H-N<), 32 (-S-CH_2-), 172.5 (cyclic, >$C_{4'}$=O), 168 (amide, >C=O), 58.2 (-CH_2-thiazolidinone), 157.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics), 35.7 ($CH_3OC_6H_4$-); MS (*m/z*): 431[M^+] ($C_{19}H_{17}N_3O_3S_3^+$), 223 ($C_{10}H_{13}O_2N_2S^+$), 208 ($C_9H_4ONS_2^+$), 195 ($C_9H_{13}ON_2S^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\ N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (4g). Brownish yellow solid, m.p.: 208 ºC; Anal.: Calcd. for $C_{19}H_{17}N_3O_3S_3$: C, 52.86; H, 3.90; N, 9.02. Found: C, 52.88; H, 3.92; N, 9.04%; IR: ν (cm^{-1}) 3378, 1339 (-NH-), 1675 (>C=O, amidyl), 1721 (>C=O, cyclic), 2830 (Ar-OCH_3); ^{1}H NMR: δ (ppm): 8.53 (s, 1H, -CONH-), 6.65-7.77 (m, 8H, Ar-H), 3.16 (s, 1H, -N=CH-), 4.29 (s, 2H, S-CH_2-), 3.66 (s, 2H, -CH_2-thiazolidinone), 3.89 (s, 3H, -OCH_3); ^{13}C NMR: δ (ppm) 127.8 (C_1), 129.7 (C_2, C_6),124.9 (C_3, C_5), 152.2 (C_4), 54.1 (>$C_{2'}$H-N<), 33 (-S-CH_2-), 171.5 (cyclic, >$C_{4'}$=O), 167 (amide, >C=O), 57.2 (-CH_2-thiazolidinone), 156.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics), 34.7 ($CH_3OC_6H_4$-); MS (*m/z*): 430[M^+] ($C_{19}H_{17}N_3O_3S_3^+$), 222 ($C_{10}H_{13}O_2N_2S^+$), 208 ($C_9H_4ONS_2^+$), 207 ($C_{10}H_{12}O_2NS^+$), 194 ($C_9H_{13}ON_2S^+$), 180 ($C_8H_4NS_2^+$), 179 ($C_9H_{12}ONS^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\ N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(2-chlorophenyl)-1,3-thiazolidin-4-one (4h). Light brown solid, m.p.: 211 ºC; Anal.: Calcd. for $C_{18}H_{14}N_3O_2S_3Cl$: C, 49.61; H, 3.23; N, 9.66. Found: C, 49.59; H, 3.21; N, 9.64%; IR: ν (cm^{-1}) 3385, 1340 (-NH-), 1678 (>C=O, amidyl), 1722 (>C=O, cyclic), 835 (Ar-Cl); ^{1}H NMR: δ (ppm) 8.50 (s, 1H, -CONH-), 6.72-7.82 (m, 8H, Ar-H), 3.17 (s, 1H, -N=CH-), 4.38 (s, 2H, S-CH_2-), 3.65 (s, 2H, -CH_2-thiazolidinone); ^{13}C NMR: δ (ppm) 128.8 (C_1), 128.7 (C_2, C_6),125.9 (C_3, C_5), 151.2 (C_4), 54.3 (>$C_{2'}$H-N<), 33.2 (-S-CH_2-), 171.7 (cyclic, >$C_{4'}$=O), 167.2 (amide, >C=O), 57.4 (-CH_2-thiazolidinone), 156.7 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 435.5[M^+] ($C_{18}H_{14}N_3O_2S_3Cl^+$), 228 ($C_9H_{10}ON_2SCl^+$), 213 ($C_9H_9ONSCl^+$), 208 ($C_9H_4ONS_2^+$), 200 ($C_8H_{10}N_2SCl^+$), 185 ($C_8H_9NSCl^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\ N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(3-chlorophenyl)-1,3-thiazolidin-4-one (4i). Light brown powder, m.p.: 226 ºC; Anal.: Calcd. for $C_{18}H_{14}N_3O_2S_3Cl$: C, 49.54; H, 3.16; N, 9.60. Found: C, 49.57; H, 3.18; N, 9.62%; IR: ν (cm^{-1}) 3380, 1341 (-NH-), 1673 (>C=O, amidyl), 1719 (>C=O, cyclic), 825 (Ar-Cl); ^{1}H NMR: δ (ppm) 8.48 (s, 1H, -CONH-), 7.15-7.92 (m, 8H, Ar-H), 3.18 (s, 1H, -N=CH-), 4.41 (s, 2H, S-CH_2-), 3.61 (s, 2H, -CH_2-thiazolidinone); ^{13}C NMR: δ (ppm) 127.7 (C_1), 129.8 (C_2, C_6),124.8 (C_3, C_5), 152.3 (C_4), 53.2 (>$C_{2'}$H-N<), 34.3 (-S-CH_2-), 170.6 (cyclic, >$C_{4'}$=O), 168.3 (amide, >C=O), 58.3 (-CH_2-thiazolidinone), 157.8 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 436[M^+] ($C_{18}H_{14}N_3O_2S_3Cl^+$), 229 ($C_9H_{10}ON_2SCl^+$), 214 ($C_9H_9ONSCl^+$), 208 ($C_9H_4ONS_2^+$), 201 ($C_8H_{10}N_2SCl^+$), 186 ($C_8H_9NSCl^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3O\ N_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

3-{[2-(Benzothiazol-2-ylthio)ethyl]amino}-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (4j). Deep brown crystal, m.p.: 219 ºC; Anal.: Calcd. for $C_{18}H_{14}N_3O_2S_3Cl$: C, 49.63; H, 3.26; N, 9.68. Found: C, 49.61; H, 3.23; N, 9.66%; IR: ν (cm^{-1}) 3383, 1342 (-NH-), 1668 (>C=O, amidyl), 1718 (>C=O, cyclic), 831 (Ar-Cl); ^{1}H NMR: δ (ppm) 8.51 (s, 1H, -CONH-), 6.96-7.86 (m, 8H, Ar-H), 3.11 (s, 1H, -N=CH-), 4.40 (s, 2H, S-CH_2-), 3.58 (s, 2H, -CH_2-thiazolidinone); ^{13}C NMR: δ (ppm) 126.8 (C_1), 128.9 (C_2, C_6), 123.9 (C_3, C_5), 151.4 (C_4), 52.3 (>$C_{2'}$H-N<), 33.4 (-S-CH_2-), 169.7 (cyclic, >$C_{4'}$=O), 167.4 (amide, >C=O), 57.4 (-CH_2-thiazolidinone), 156.7 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics); MS (*m/z*): 434[M^+] ($C_{18}H_{14}N_3O_2S_3Cl^+$), 226 ($C_9H_{10}ON_2SCl^+$), 211 ($C_9H_9ONSCl^+$), 208 ($C_9H_4ONS_2^+$), 201 ($C_8H_{10}N_2SCl^+$), 198 ($C_8H_9NSCl^+$), 182 ($C_8H_9NSCl^+$), 180 ($C_8H_4NS_2^+$), 166 ($C_7H_2NS_2^+$), 134 ($C_7H_2NS^+$), 122 ($C_6H_2NS^+$), 115 ($C_3H_3ON_2S^+$), 108 ($C_6H_2S^+$), 90 ($C_6H_2N^+$).

Antimicrobial Activity

Compounds **4a-j** were screened for their antibacterial activity against *Bacillus subtilis* (ATCC-6633), *Staphylococcus aureus* (ATCC-6538) and *Escherichia coli* (ATCC-8739) and antifungal activity against *Candida albicans* (ATCC-64550), *Candida krusei* (ATCC-14243) and *Candida parapsilosis* (ATCC-22019) by filter paper disc technique [20]. Standard antibacterial streptomycin and antifungal griseofulvin were also tested under similar conditions for comparison.

RESULTS AND DISCUSSION

Conventional methodology sometimes has lower yields than microwave protocols. Microwave irradiation facilitates

Table 1. Comparison of Microwave and Conventional Techniques (compounds **4a-j**)

Entry	Substitutents -R	Microwave method				Conventional method	
		Time (min)	Power (watts)	Constant temperature (°C)	Yield (%)[a]	Time (h)	Yield (%)[a]
4a	4-NO_2	3.0	400	146	86	8.0	68
4b	3,4,5-$(OCH_3)_3$	2.0	500	150	95	7.0	71
4c	2-OH	2.5	450	148	89	7.5	66
4d	3-OH	2.5	450	148	89	7.5	76
4e	4-OH	2.0	500	150	95	7.0	71
4f	2-OCH_3	3.0	400	146	86	8.0	59
4g	4-OCH_3	2.5	450	148	89	7.5	62
4h	2-Cl	2.0	500	146	95	8.0	72
4i	3-Cl	2.5	450	144	89	8.5	74
4j	4-Cl	3.0	400	146	86	8.0	70

[a]Yield of isolated products.

the polarization of the molecule under irradiation causing a rapid reaction to occur. A comparative study in terms of yield and reaction period is shown in Table 1. All the compounds synthesized were adequately characterized by elemental analysis and spectral data. The MS fragmentation pattern is presented (Fig. 2) as an additional evidence for the proposed structure of **4a**.

2-Mercaptobenzothiazole and ethyl chloroacetate in the presence of anhydrous K_2CO_3 in dry acetone as a reaction mediator afforded ethyl 2-(benzothiazolylthio)acetate **1**. The formation of compound **1** was evidenced by the appearance of signal at 1.23 and 4.13 ppm due to C*H*$_3$ and C*H*$_2$ respectively in -$COOCH_2CH_3$ (*J* = 7 Hz) ethyl 2-(benzothiazolylthio)acetate **1** in ^{1}H NMR spectra and IR spectra bands due to 1723 cm^{-1} (>C=O of ester) and 2915, 2871, 1423, 713 cm^{-1} (CH_2 and CH_3) also confirmed the formation of compound **1**. Compound **1** and hydrazine hydrate in ethanol as a reaction media afforded 2-(benzothiazol-2-ylthio)acetohydrazide **2**. In the ^{1}H NMR spectra of **2,** a peak at δ 7.88 ppm was observed due to -CONH - and a peak at δ 4.40 ppm was due to -NH_2. Furthermore, in the IR spectra, the bands at 1665 cm^{-1} (>C=O of amide) and 3352, 3378 cm^{-1} (-$NHNH_2$) also confirm the formation of compound **2**. Compound **2**, aromatic aldehyde and 2-3 drops of glacial acetic acid in ethanol as a reaction mediator afforded 2-(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide **3**. The formation of **3** was evidenced by the appearance of signal at 4.40 ppm due to -N=CH-. In the ^{1}H NMR spectra, the appearance of signal at 60 ppm was due to >CH-N<. In the ^{13}C NMR spectra and IR spectra bands, due to (-N=CH-) at 1626 cm^{-1}, also confirmed the formation of **3**. Compound **3**, thioglycollic acid and anhydrous $ZnCl_2$ in DMF as a reaction mediator afforded thiazolidinone **4**. In the ^{1}H NMR spectra of **4a**, the peak at δ 3.60 ppm was observed due to CH_2 in the thiazolidinone ring; in the ^{13}C NMR spectra of **4a**, the peak at δ 30 ppm was observed due to CH_2, 172.5 ppm (cyclic, >C=O) and 157.5 ppm (heteroaromatics) in the thiazolidinone ring. In the IR spectra of **4a,** the bands at 1717 cm^{-1} (>C=O, cyclic) also confirmed the formation of thiazolidinone **4a**. In the mass spectra of **4a,** the molecular ion peak at 446 [M^+] also confirmed the formation of thiazolidinone. The fragment ion (m^+) peak was observed at 238 *m/z* ($C_9H_8O_3N_3S^+$), 223 *m/z* ($C_9H_7O_3N_2S^+$), 210 *m/z* ($C_8H_8O_2N_3S^+$), 208 *m/z* ($C_9H_6ONS_2^+$), 195 *m/z* ($C_8H_7N_2O_2^+$), 180 *m/z* ($C_8H_6NS_2^+$), 166 *m/z* ($C_7H_4NS_2^+$), 134 *m/z* ($C_7H_4NS^+$), 115 *m/z* ($C_3H_3N_2OS^+$), 122 *m/z* ($C_6H_4NS^+$), 108 *m/z* ($C_6H_4S^+$) and 90 *m/z* ($C_6H_4N^+$) by the loss of fragment radicals and neutrals •CO (-28), •NH (-15), •$C_6H_5NO_2$ (-123), •CH_2 (-14), •CNS (-58), •CS_2 (-76), •S (-32) and •CS (-44).

All the reactions that used microwave irradiation were completed in 3-5 min, whereas similar reactions under conventional heating (steam bath) at similar temperatures (80-100 ^{o}C) gave poor yields with comparatively longer reaction time periods (Table 1), demonstrating that the effect of microwave irradiation is not purely thermal. Microwave irradiation facilitates the polarization of the molecules under

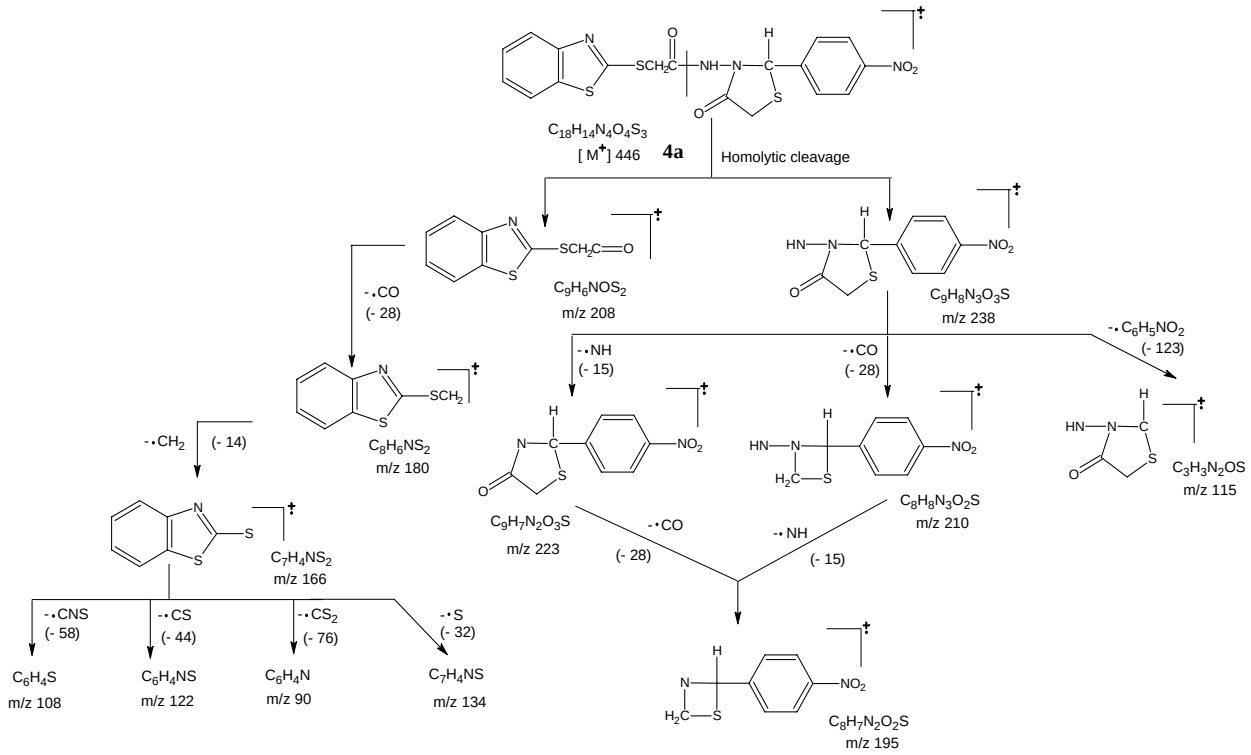

Fig. 2. Fragmentation pattern of 2-(4-Nitrophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines **4a**.

irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state [19]. The effectiveness of microwave irradiation and conventional heating for the synthesis of compounds **4a-j** has been compared (Table 1). Under microwave irradiation conditions, the yields of **4a-j** are high (95-86%), whereas using conventional heating the yields are only 59-76%. The effects of irradiation power and time on the reaction were also studied and the results summarized in Tables 2 and 3. High yields of compounds **4a-j** were obtained at 500 W for 2.0 min under microwave irradiation.

The antimicrobial screening results, presented in Table 4, reveal that compounds **4d** and **4f** exhibited a significant activity against *E. coli*. Compounds **4c** and **4b** showed promising activity against *S. aureus* and *B. subtilis*, respectively. While the compounds **4a**, **4e**, **4g**, **4h** and **4j** exhibited highest activity against both *S. aureus* and *B. subtilis*. Similarly, compounds **4a**, **4b**, **4e**, **4g**, **4i** and **4j** showed highest degree of inhibition against *C. albicans*, *C. krusei* and *C. parapsilosis*. However, the activities of all the tested compounds are less than that of standards.

In conclusion, this new method for the synthesis of 4-thiazolidinones using anhydrous $ZnCl_2$ as a catalyst in DMF under microwave irradiation offers significant improvements over existing procedures. Also, this simple and reproducible technique affords various 4-thiazolidinones with short reaction times, excellent yields, and without the formation of undesirable by-products.

Table 2. The Effect of Microwave Irradiation Power[a]

Irradiation power (watts)	300	350	400	450	500
Yield (%)	80	83	86	89	95

[a] Irradiation time is 2.0 min.

Table 3. The Effect of Microwave Irradiation Time[a]

Irradiation time (min)	4.5	4.0	3.0	2.5	2.0
Yield (%)	80	83	78	89	95

[a] Irradiation power is 500 watts.

Table 4. Antimicrobial Activity of Compounds **4a-j**

Compound	Antibacterial activity			Antifungal activity		
	B. subtilis	*S. aureus*	*E. coli*	*C. albicans*	*C. krusei*	*C. parapsilosis*
4a	++	++	++	++	++	++
4b	-	-	-	++	++	++
4c	++	++	++	-	-	-
4d	+	+	+++	+	+	++
4e	++	++	++	++	++	++
4f	+	+	+++	+++	+	+++
4g	++	++	++	++	++	++
4h	++	++	++	-	-	-
4i	-	-	-	++	++	++
4j	++	++	++	++	++	++
Zone of Inhibition of Standard Drugs						
Streptomycin	++++	++++	++++			
Griscofulvin				++++	++++	++++

Zone of inhibition: (-) 6 mm; (+) 6-15 mm; (+ +) 15-20 mm; (+ + +) 20-25 mm; (+ + + +) 25-30 mm.

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