Microwave Assisted One Pot Synthesis of Some 2-(Substituted) Phenyl-3-Pyridin-2-y1,3-Thiazolidin-4-Ones Under Solvent Free Conditions

Maruti S. Kanase, Pravina B. Piste*
P.G. Department of Chemistry, Y. C. Institute of Science, Satara, Dist: Satara (Maharashtra), India.
*Corresponding author’s E-mail: ppiste321@gmail.com

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ABSTRACT
We have reported an efficient, operationally simple, environmental benign one pot synthesis of Some 2-(Substituted) Phenyl-3-Pyridin-2-y1,3-Thiazolidin-4-Ones Under Solvent Free Conditions (a-f) by a mixture of equimolar quantities of 2-amino pyridine, substituted benzaldehyde and thioglycolic acid with a pinch of anhydrous zinc chloride was heated in a microwave oven for 10-15 min. The progress of the reaction was monitored by TLC. The yields were in the range of 61-86 %. Synthesized compounds were screened for antimicrobial activities against E. coli as Gram negative bacteria and S. aureus as Gram positive bacteria. Some of the compounds displayed pronounced biological activity. The structures of synthesized compounds were elucidated on the basis of spectral (¹H NMR, ¹³C NMR and IR ) and elemental analysis.

Keywords: Microwave, Thiazolidine, 2-amino pyridine, Antimicrobial activity.

INTRODUCTION
Thiazolidin-4-one exhibits wide spectrum of biological profile such as anti-inflammatory and analgesic⁵, antidiabetes⁶, antituberculosis⁷, anti-HIV⁸, antitumor⁹, antioxidant⁹, antifungal¹⁰. In addition to this pyridine derivatives are also known to possess antimicrobial activities. Recent literature shows that if these two moieties are coupled together, there is enhancement in the biological responses. So our curiosity was to find the result of accommodating these two heteroaryl fragments in a single molecular framework on their biological activities.

Recently the greener approach like microwave heating, ultra-sonication, one pot and solvent free organic synthesis is gaining impetus due to the advantages such as easy work up of the products, no need of added unit operations (isolating and purifying the intermediates), rapid reactions and mild conditions. Hence, we have carried out synthesis of a few 2-(substituted) phenyl -3-pyridin-2-y1, 3-thiazolidin-4-one derivatives under solvent free condition in one pot microwave irradiation method.

MATERIALS AND METHODS
All chemicals were of synthetic grade (S.D. Fine. Chem. Ltd. Mumbai, India). Melting points were determined by open capillary method and are uncorrected. Products were recrystallized from ethanol as a solvent. The purity of compound checked by the TLC plate method (Pet ether: Ethyl acetate, 9:1, v/v). The compounds were characterized by using IR, ¹H NMR and C¹³ spectral analysis. The IR spectra were recorded on Perkin –Elmer spectrum in form of KBr pellet. ¹H NMR was recorded in CDCl₃ on Perkin Elmer R-32 spectrum using TMS as internal standard. All the compounds were analyzed for C, H and N on Carlo-Erba elemental analyzer .The synthesized samples were purified by using Column chromatography (Pet ether and Ethyl acetate system) and recrystallized from ethanol.

General procedure for Synthesis of 2-(substituted ) phenyl-3-pyridin-2-y1,3-thiazolidin-4-one derivatives (a-f):
To the mixture of a heterocyclic amine (1mmol), substituted aromatic aldehyde (1mmol), and thioglycolic acid (1mmol) taken in beaker, a pinch of anhydrous zinc chloride was added. The mixture was irradiated in microwave oven for 10 minutes. The progress of the reaction was monitored by TLC and the reaction mixture was further irradiated for 3-5 min more (depending on the need). The final product was cooled and poured in ice, filtered, washed with water and dried.

RESULTS AND DISCUSSION
The desired products were prepared in good yield (61 -86 %) in very short time (10 -15min.) by employing eco-friendly route (Microwave irradiation, one pot synthetic method). The condensation cyclisation of 2-amino pyridine, substituted benzaldehyde and thioglycolic acid was carried out in solvent free condition using zinc chloride as a dehydrating agent. The structures of the newly synthesized compounds were confirmed on the basis of IR, NMR, Mass spectral and elemental analysis. The completion of reaction was monitored by TLC by using n-hexane and ethyl acetate as solvent system .The reagents utilized in the proposed method are readily available and did not involve any critical reaction conditions or tedious sample preparation. (Scheme)
The products were characterized by melting points and Rf values by using ethyl acetate (20%) and n-hexane (80%) as a solvent system. The synthesized derivatives were established on the basis of spectral studies. Formation of thiazolidinone was indicated and confirmed by the appearance of singlet at 4.0 ppm due to cyclic-CH₂ in 1H NMR and absorption band at 1671 cm⁻¹ due to >C=O (amido) stretching frequency in IR spectrum. Formation of products, III a-c was indicated by IR band at 1467 cm⁻¹ due to NO₂.

The yielded derivatives were screened for Gram positive bacteria, staphylococcus aureus and Gram negative bacteria viz. Escherichia coli by measuring the zone of inhibition at concentrations of 100 mg/ml. The standard used for comparison was streptomycin. The compounds d, e, and f with electron withdrawing groups at position 4, in C-2 aryl substituent exhibited excellent activity against S. aureus while compound c showed moderate activity. All of the synthesized compounds from the list exhibited very poor response against Gram negative bacteria, E.Coli.

### Table 1: Physical and Analytical data of 2, 3-(substituted) diaryl-1,3-thiazolidine-4-ones (a-f):

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>-R</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Spectral Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-NO₂</td>
<td>165</td>
<td>80</td>
<td>IR (KBr): 2963(CH₃), 1671(C=O), 1467(NO₂) cm⁻¹ NMR (DMSO): δ: 7.0-7.7(m, 8H; Ar-H), 6.9(s, 1H, CH), 4.0 (s, 2H, CH₂) ppm. 13C-NMR (DMSO): δ: 171.30, 147.65, 145.20, 138.93, 131.14, 130.26, 130.18, 129.32, 128.18, 127.19, 124.78, 115.78, 33.02.</td>
</tr>
<tr>
<td>b</td>
<td>3-NO₂</td>
<td>152</td>
<td>71</td>
<td>IR (KBr): 3067(CH₃), 1675(C=O), 1467(NO₂) cm⁻¹ 1H-NMR(DMSO) δ: 7.7-8.0(m, 8H; Ar-H), 6.2(1H, CH), 3.8(s, 2H, CH₂) ppm. 13C-NMR (DMSO): δ: 171.32, 147.42, 144.35, 138.82, 133.85, 129.82, 129.35, 129.18, 128.94, 127.19, 123.85, 117.82, 32.96.</td>
</tr>
<tr>
<td>c</td>
<td>4-NO₂</td>
<td>161</td>
<td>86</td>
<td>IR (KBr): 3067(CH₃), 1675(C=O), 1467(NO₂) cm⁻¹ 1H-NMR(DMSO) δ: 7.7-8.0(m, 8H; Ar-H), 6.2(1H, CH), 3.8(s, 2H, CH₂) ppm. 13C-NMR (DMSO): δ: 171.32, 147.42, 144.35, 138.82, 133.85, 129.82, 129.35, 129.18, 128.94, 127.19, 123.85, 117.82, 32.96.</td>
</tr>
<tr>
<td>d</td>
<td>4-F</td>
<td>95</td>
<td>62</td>
<td>IR (KBr): 3067(CH₃), 1675(C=O) cm⁻¹ 1H-NMR(DMSO) δ: 7.7-8.0(m, 8H; Ar-H), 6.2(1H, CH), 3.8(s, 2H, CH₂) ppm. 13C-NMR (DMSO): δ: 171.32, 147.42, 144.35, 138.82, 133.85, 129.82, 129.35, 129.18, 128.94, 127.19, 123.85, 117.82, 32.96.</td>
</tr>
<tr>
<td>e</td>
<td>4-Cl</td>
<td>112</td>
<td>78</td>
<td>IR (KBr): 3067(CH₃), 1675(C=O) cm⁻¹ 1H-NMR(DMSO) δ: 7.0-7.7 (m, 8H; Ar-H), 6.9 (1H, CH), 4.0 (s, 2H, CH₂) ppm. 13c-NMR (DMSO), δ: 171.32, 147.42, 144.35, 138.82, 133.85, 129.82, 129.35, 129.18, 128.94, 127.19, 123.85, 117.82, 32.96.</td>
</tr>
<tr>
<td>f</td>
<td>4-Br</td>
<td>126</td>
<td>81</td>
<td>IR (KBr): 2963(CH₃), 1671(C=O) cm⁻¹ 1H-NMR(DMSO) δ: 7.0-7.7 (m, 8H; Ar-H), 6.9 (1H, CH), 4.0 (s, 2H, CH₂) ppm. 13C-NMR (DMSO), δ: 171.30, 147.65, 145.20, 138.93, 131.14, 130.26, 130.18, 129.32, 128.18, 127.19, 124.78, 115.78, 33.02.</td>
</tr>
</tbody>
</table>

### Table 2: Antibacterial activity of Synthesized Compounds (a-f):

<table>
<thead>
<tr>
<th>Comp. (100µg/ml)</th>
<th>Antibacterial Activity (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S. aureus</td>
</tr>
<tr>
<td>a</td>
<td>12</td>
</tr>
<tr>
<td>b</td>
<td>10</td>
</tr>
<tr>
<td>c</td>
<td>16</td>
</tr>
<tr>
<td>d</td>
<td>20</td>
</tr>
<tr>
<td>e</td>
<td>18</td>
</tr>
<tr>
<td>f</td>
<td>18</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>23</td>
</tr>
</tbody>
</table>

### Comparison Chart

![Antibacterial activity of Synthesized compounds with standard drug](image)
CONCLUSION

We have carried out the synthesis of some 1,3-Thiazolidin-4-One derivatives by modern techniques.

The merits of the current protocols are,

1. One pot synthesis
2. Environmental benign methodology i.e. Microwave irradiation
3. Shorter reaction time
4. Solvent free condition
5. Operationally simple and efficient technique
6. Atom economy
7. Good antibacterial activity
8. high purity and needed no separation

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REFERENCES


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