An expedient solvent-free synthesis of 
(Z)-2-alkylidene-4-oxothiazolidine derivatives 
under microwave irradiation

Rade Marković,* a,b Miodrag M. Pergal,a Marija Baranac,a Dragomir Stanisavljev,c and 
Milovan Stojanovicb

a Faculty of Chemistry, University of Belgrade, Studentski trg 16 P. O. Box 158, 11001 Belgrade, 
Serbia and Montenegro; b Center for Chemistry ICTM, P. O. Box 473, 11000 Belgrade, Serbia and 
Montenegro; c Faculty of Physical Chemistry, University of Belgrade, Studentski trg 16, 11001 
Belgrade, Serbia and Montenegro
E-mail: markovic@helix.chem.bg.ac.yu
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Abstract
A new and efficient microwave-assisted synthesis of (Z)-2-alkylidene-4-oxothiazolidine derivatives 
4 under solvent-free conditions and without solid support, is described. In comparison to 
conventional technique, experimental evidence reveals the benefits of the MW-promoted synthesis 
of functionalized 4-oxothiazolidine derivatives 4 in terms of simple workup, efficiency and safe 
reproducibility. The method, as environmentally cleaner, was shown to be potentially applicable to 
similar chemical processes, such as the preparation of not easily obtainable 4-oxo-1,3-thiazinan-2-
ylidene derivative 6.

Keywords: 4-Oxothiazolidine, β-enamines, microwave irradiation, solvent-free synthesis

Introduction

The advantages of numerous microwave (MW)-induced reactions over conventional reactions, and 
their utility in organic synthesis, have been fully recognized in the last two decades.¹ Well-known 
applications of the MW methodology involve the effective syntheses and functionalization of 
various and structurally diverse heterocyclic compounds.² Among them, a few examples of MW-
assisted syntheses of a series of 2-substituted 4-thiazolidinones, based exclusively on the 
condensation-cyclization sequence employing a three-component reaction mixture of a substituted 
acyclic or aromatic primary amine or diamine, aldehyde and mercaptoacetic acid, have been 
described.³ Other common methods to construct a 4-oxothiazolidine skeleton, for example, (i) by 
treatment of α-haloalkanoic acids and their derivatives,⁴ or dimethyl acetylenedicarboxylate⁵ with 
substituted thioureas, (ii) from ammonium dithiocarbamates and glycidic esters,⁶ or (iii) by one-pot
cyclization of arylacetonitriles with N-phenylisothiocyanate and ethyl 2-chloro-2-oxoacetate, are limited to classical liquid-phase synthesis.

In a continuation of our studies on the chemistry of heterocyclic enaminoones and enaminoitriles, containing the 4-oxothiazolidine moiety which is of broad synthetic and biological relevance, we wish to report the first dry-media microwave synthesis of β-enamino-type (Z)-4-oxothiazolidine derivatives (Scheme 1), from activated nitriles 1 and α-mercaptoesters 2.

Literature search indicates that only two examples of microwave synthesis of the heterocyclic compounds possessing the exocyclic C=C bond, i.e., 4-alkylidene-1H-imidazol-5(4H)-ones and 2-phenyl-4-arylidene-5(4H)-oxazolones, have been reported so far.

\[
\begin{align*}
N=C & \\
1 & \quad + \\
& \quad R^1\ \text{EtO}\ HN \quad \text{EWG} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
these of the conventional method. Moreover, preliminary reactions (entries 8 and 9) carried out in the unmodified domestic oven, applying 50% of the max. power of 750 W (Method B), afforded, after only 10 seconds, the desired 4-oxothiazolidines 4h and 4i in high yields, practically without side products.

Table 1. Synthesis of 4-oxothiazolidines 4 by conventional method and under MW irradiation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>EWG</th>
<th>R₁</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conventional Method&lt;sup&gt;b&lt;/sup&gt;</th>
<th>MW Method&lt;sup&gt;c&lt;/sup&gt;</th>
<th>MW Method&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>COPh</td>
<td>CH₂CO₂Et</td>
<td>68</td>
<td>59</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>COPh</td>
<td>H</td>
<td>79</td>
<td>20</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>COPh</td>
<td>CH₃</td>
<td>63</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>CO₂Et</td>
<td>CH₂CO₂Et</td>
<td>62</td>
<td>86</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>CO₂Et</td>
<td>H</td>
<td>67</td>
<td>95</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>CO₂Et</td>
<td>CH₃</td>
<td>59</td>
<td>69</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>CN</td>
<td>CH₂CO₂Et</td>
<td>68</td>
<td>88</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>CN</td>
<td>H</td>
<td>68</td>
<td>88</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>CN</td>
<td>CH₃</td>
<td>75</td>
<td>78</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>CONHPh</td>
<td>CH₂CO₂Et</td>
<td>77</td>
<td>49</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4k</td>
<td>CONHPh</td>
<td>H</td>
<td>97</td>
<td>66</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4l</td>
<td>CONH(CH₂)₂Ph</td>
<td>CH₂CO₂Et</td>
<td>60</td>
<td>63</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4m</td>
<td>CONH(CH₂)₂Ph</td>
<td>H</td>
<td>83</td>
<td>86</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4n</td>
<td>CONH(CH₂)₂Ph</td>
<td>CH₃</td>
<td>80</td>
<td>66</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Products purified by chromatography; the spectroscopic data of compounds 4a-b and 4d-l were identical with these of the authentic samples prepared previously by conventional method.<sup>12</sup>

<sup>b</sup> Rxn. time: 2-9 h; molar ratio 1/2=1/1 to 1/1.7; solvent: EtOH; catalyst: K₂CO₃.

<sup>c</sup> Method A: Single mode MW irradiation at 80 °C and 150 W power for 2 min.; molar ratio 1/2=1/1.1.

<sup>d</sup> Method B: MW irradiation applying 50-100% of the maximum power (750 W), for 10-150 seconds; in some cases sequential irradiations (30 seconds each) were applied for the total time (150 seconds).

The multiple rate enhancement reflects obviously the faster heating of the reaction mixture due to the increased microwave power. However, in terms of the polar mechanism, depicted in Scheme 1, the stereoselective synthesis of (Z)-4-oxothiazolidine derivatives 4 is thought to be a perfect case for the observation of the specific MW effect.<sup>1</sup> Namely, based on our calculations using the MNDO-PM3 method, it has been established that in the conventional synthesis of (Z)-4-oxothiazolidine derivatives 4 the ring-formation (step 3→4) occurs via the anionic intermediate 3.<sup>14</sup> As a consequence, the polarity of the system increases during the reaction course from reactants 1.
and 2 to the more stabilized transition state, that structurally resembles the anionic species 3. Therefore, an expected decrease in the activation energy of the MW-initiated reactions, correlates with the strong rate acceleration. The two-step one-pot reaction (Scheme 1), proceeded under precise temperature and power settings with a diverse range of reactants 1 and 2, indicating the generality of the method A. In the case of 4-oxothiazolidines 4j-n, reactions took place at the temperature well below the melting points of the starting nitriles 1. Synthesis of compounds 4 in the house microwave oven occurred with equal facility (Table 1; last column). All of the above examples, unlike the classical method, refer to the solvent-free synthesis of 4-oxothiazolidines 4 without solid support. In contrast to the accelerated MW synthesis, the conventional one, which does not proceed without solvent, requires, under the optimized conditions, drastically longer reaction times (2-9 h) and the use of a larger molar excess of the mercapto reactant 2 relative to nitrile 1 (Table 1, column V). As can be seen graphically in Figure 1, only MW-assisted reaction of 1 (EWG = COPh) and 2 (R² = CH₃) did not effectively proceed under the usual reaction conditions, 4c being formed in low 10% yield. In both cases, in addition to the products 4b and 4c, the corresponding reactants were recovered. Interestingly, the cyclized product 4b was produced in a satisfactory yield (50%) using the domestic MW unit (Method B), but under the focused irradiation (Method A) the yield was only 20%.

![Figure 1. Yield comparison of 4-oxothiazolidines 4 by conventional procedure and MW methods A and B.](image)

In all conventional syntheses, as established in earlier studies, and in syntheses under the influence of microwaves as well, the products 4 were isolated as the single (Z)-isomers. An exception refers to the Z,E-mixtures in the case of 4-oxothiazolidines 4, containing the nitrile group attached to the exocyclic C=C bond (entries 7-9). In addition, the heterocyclization step, occurring through in situ formed intermediate 3 (with EWG = CH₂CO₂Et), proceeded in a regiospecific manner to give only 2-alkylidene-4-oxothiazolidines. An alternative mode of intramolecular
cyclization, leading to the concurrent six-membered ring 4-oxo-1,3-thiazinane derivatives, was not observed.

Noteworthy in this context is the possibility to carry out time-controlled microwave synthesis of thiazinane-type products \( \text{6} \)\(^{11} \) with the \( \beta \)-mercapto-substituted substrates and nitriles \( \text{1} \) (Scheme 2). For instance, when malononitrile was reacted with an equimolar amount of \( 3 \)-mercaptopropanoate with 5 mol % of \( \text{K}_2\text{CO}_3 \) as a catalyst in ethanol, under focused microwave irradiation for 10 minutes, the corresponding 2-(4-oxo-1,3-thiazinan-2-ylidene)acetonitrile (\( \text{6; EWG} = \text{CN} \)) was obtained in 27% yield. In sharp contrast, the reaction of \( \text{5} \) with ethyl cyanoacetate under the thermal heating in ethanol solution led to a complex mixture, whereas the expected product \( \text{6} \) (\( \text{EWG} = \text{CO}_2\text{Et} \)) was isolated in negligible yield (3%).

**Scheme 2**

Furthermore, shorter microwave exposure of the same reaction mixture (2 minutes), in the presence of the large excess of the reactant \( \text{5} \) (Scheme 2), yielded in moderate yield the addition product, ethyl 3-amino-3-(2-ethoxycarbonylethylsulfanyl)propenoate (\( \text{7} \)), that is the intermediate leading to ethyl (4-oxo-1,3-thiazinan-2-ylidene)ethanoate (\( \text{6; EWG} = \text{CO}_2\text{Et} \)). Under the reaction conditions employed, the heterocycle \( \text{6} \) was not detected even in minute quantities. The lack of cyclization of \( \text{7} \) into the cyclic compound \( \text{6} \) can be adequately explained by taking into account the stability of \( \text{7} \) due to the formation of intramolecular hydrogen bond between the proximal amino and ester groups. However, the isolation of \( \text{7} \) under these reaction conditions is another comparative advantage of the microwave-controlled reaction. This indicates that MW procedure could be adaptable to a wide range of similar processes giving rise to heterocyclic compounds of synthetic and biological interest.

In summary, we have demonstrated the feasibility of regio- and stereoselective MW-induced synthesis of a series of (\( Z \))-2-alkylidene-4-oxothiazolidines from activated \( \beta \)-oxonitriles \( \text{1} \) and \( \alpha \)-mercaptoesters \( \text{2} \). In comparison to classical synthesis, the method is simpler, faster and environmentally cleaner, as no organic solvent and/or solid support have been employed during the reaction course.
Experimental Section

General Procedures. Typical experimental procedure for the reactions carried out in a CEM Focused Microwave Synthesizer (Method A): thoroughly mixed neat nitrile 1 (1 mmol), mercapto reactant 2 (1.1 mmol) and potassium carbonate (2% mol equivalent) were placed in a glass vial containing a small stirring bar. The glass vial was sealed and exposed to microwaves (150 W) at 80 °C for 2 minutes. After cooling to room temperature, the progress of the reaction was checked by TLC. In two cases during the unsatisfactory synthesis of 4b and 4c, as indicated by the presence of appreciable amounts of reactants, the reaction mixture was irradiated again for another 2 min, however without result in terms of better yields. In all other cases the reaction mixture was dissolved in an appropriate solvent (ethyl acetate, ethanol or acetonitrile) filtered and concentrated however without result in terms of better yields. In all other cases the reaction mixture was made on the basis of spectroscopic data (IR, 1H and 13C NMR, MS, UV) and elemental analysis. Analytically pure samples were obtained by crystallization from ethanol.

(Z)-(5-Methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (4c). Mp 209-211 °C; IR (CHCl3, cm⁻¹) 3254, 3082, 1708, 1627, 1598, 1576, 1522, 1453, 1370, 1309, 1250, 1181, 813, 780, 748 and 698; 1H-NMR (200 MHz; DMSO-d₆) 1.50 (3 H d, J 7.2, CH₃), 4.08 (1 H, q, J 7.2, CHS), 6.80 (1 H, s, =CH), 7.48-7.63 (3 H, m, -phenyl), 7.83-7.87 (2 H, m, o-phenyl), 11.80 (1 H, s, NH); 13C-NMR (50 MHz; DMSO-d₆) 18.3 (CH₃), 41.0 (CHS), 94.5 (=CH), 127.3 (o-phenyl), 129.0 (m-phenyl), 132.3 (p-phenyl), 138.5 (C1-phenyl), 160.6 (C=), 174.3 (CO-ester); MS m/z: 234 (M + 1); UV λmax(DMSO)/nm 335 (ε=3 mol⁻¹ cm⁻¹ 23 300); Anal. Calc. for C₁₃H₁₁NO₂S: C, 61.78; H, 4.75; N, 6.00; S, 13.75%; Found: C, 61.60; H, 4.70; N, 6.03; S, 13.97%.

(Z)-(4-Oxothiazolidin-2-ylidene)-N-(2-phenylethyl)ethanamide (4m). Mp 205-206 °C; IR (CHCl₃, cm⁻¹) 3312, 3166, 3055, 1699, 1640, 1565, 1497, 1463, 1311, 1267, 1184, 886, 818, 787, 729 and 692; 1H-NMR (200 MHz; DMSO-d₆) 2.71 (2 H, t, J 7.3, CH₂Ph), 3.25-3.35 (2 H, m, NCH₂), 3.63 (2 H, s, CH₂S), 5.59 (1 H, s, =CH), 7.15-7.33 (5 H, m, Ph), 7.83 (1 H, t, J 5.4, NHamide), 11.27 (1 H, s, NHring); 13C-NMR (50 MHz; DMSO-d₆) 32.1 (CH₂S), 35.7 (CH₂Ph), 40.3 (NCH₂), 92.7 (CH, 126.3 (p-phenyl), 128.6 (o-phenyl), 128.9 (m-phenyl), 139.9 (C1-phenyl), 151.9 (C=), 166.8 (COamide), 174.3 (COring); MS m/z: 263 (M + 1); UV λmax(DMSO)/nm 283 (ε=3 mol⁻¹ cm⁻¹ 23 150); Anal. Calc. for C₁₃H₁₄N₂O₂S: C, 59.52; H, 5.38; N, 10.68; S, 12.22%; Found: C, 59.47; H, 5.38; N, 10.61; S, 12.51%.

(Z)-(5-Methyl-4-oxothiazolidin-2-ylidene)-N-(2-phenylethyl)ethanamide (4n). Mp 195 °C; IR (CHCl₃, cm⁻¹) 3295, 3084, 3054, 1702, 1644, 1576, 1499, 1456, 1374, 1314, 1275, 1184, 823, 786, 735 and 699; 1H-NMR (200 MHz; DMSO-d₆) 1.41 (3 H d, J 7.2, CH₃), 2.71 (2 H, t, J 7.3, CH₂Ph), 3.24-3.35 (2 H, m, CH₂N), 3.89 (1 H, q, J 7.2, CHS), 5.57 (1 H, s, =CH), 7.16-7.33 (5 H, m, Ph), 7.84 (1 H, t, J 5.4, NHamide), 11.23 (1 H, br s, NHring); 13C-NMR (50 MHz; DMSO-d₆) 19.0 (CH₃),...
35.6 (CH₂Ph), 40.3 (NCH₂), 40.6 (CHS), 92.7 (=CH), 126.2 (p-phenyl), 128.5 (o-phenyl), 128.8 (m-phenyl), 139.9 (C1-phenyl), 150.0 (C=), 166.6 (COamide), 176.9 (CORing); MS m/z: 277 (M + 1); UV λmax(DMSO)/nm 284 (ε/dm³ mol⁻¹ cm⁻¹ 27 200); Anal. Calc. for C₁₄H₁₄N₂O₂S: C, 60.85; H, 5.84; N, 10.14; S, 11.60%; Found: C, 60.54; H, 5.83; N, 10.11; S, 11.69%.

Acknowledgements

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References