Improved Method for the Synthesis of 1,2,4-Triazolo[4,5-a]pyrimidin-5-ones

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Abstract: Five new 1,2,4-triazolo[4,5-a]pyrimidin-5-ones were synthesised in good yield in a paste-like medium using microwave irradiation.

Keywords: microwave, paste-like medium, condensation, alcohol

Derivatives of triazolopyrimidines have antiseptic and bactericide, fungicide, herbicide, antihypertensive and diuretic activities. These properties as well as the interest in the reactivity of triazolopyrimidine derivatives initiated the search for a clean, efficacious and economic method for the synthesis of these compounds.

Generally, the synthesis of triazolopyrimidines was carried out in a liquid medium under reflux; this method is strongly pH-dependent. Moreover, the organic solvents usually employed are toxic, the reactions last many hours, and the yields are insignificant.

We have reported novel electromagnetic microwave methods which employ new absorbent supports or paste-like chemical medium. As a result of this we developed a synthesis of 3,7-dialkyl-6-ethoxycarbonyl-1-phenyl-5H-1,2,4-triazolo[4,5-a]pyrimidin-5-one derivatives 3a–e. These compounds are formed by the condensation of 5-amino-1-phenyl-1,2,4-triazoles 1a and 1b with diethyl (ethoxymethylene)malonate derivatives 2a–c (Scheme 1).

A paste-like chemical medium results by the addition of a small volume of a very polar solvent to the reaction medium; the polar solvent does not react with the reagents. The solvent which we employed to initiate the reactions under microwave irradiation was ethanol, which is also a by-product of the reaction. Molecules of ethanol absorb the microwaves and create hot spots in the reaction medium. These hot spots are like catalytic centres. As consequence of heating the solvent quickly evaporates and therefore it does not contaminate the main product. A combination of easy experimental installation, facile separation of the products, high purity of the compounds, short irradiation time and high yields are the benefits of this method.

5-Amino-1-phenyl-1,2,4-triazoles and diethyl (ethoxymethylene)malonate derivatives are commercially available substances. The obtained compounds were identified by TLC (silica gel, MeOH), elemental analyses, and 1H NMR and IR spectra. Melting points were measured on a Boëtius melting point apparatus. Elemental analyses were performed with a Carlo Erba model 1106 apparatus. IR/FT spectra were recorded on KBr pellets using a Perkin-Elmer 1600 spectrometer. 1H NMR spectra were recorded in hexadeuteroacetone solutions with TMS as internal standard on a BRUKER ARX 400 MHz spectrometer. An Optiquick Y71 microwave oven operating at 650 W was used. Temperatures after irradiation were measured using a Quick novo digital thermocouple thermometer.

3,7-Dialkyl-6-ethoxycarbonyl-1-phenyl-5H-1,2,4-triazolo[4,5-a]pyrimidin-5-one 3a–e; General Procedure

Aminotriazole (10 mmol), diethyl (ethoxymethylene)malonate derivative (15 mmol) and EtOH (few drops) were placed in a 25 mL open Pyrex beaker. The resulting paste was irradiated in a microwave oven (λ = 12.2 cm) for the required time (Table 1). After irradiation, the residue obtained was purified by recrystallisation from MeOH to give 3a–e.

Scheme 1
Table 1 Synthesis and Properties of 3,7-Dialkyl-6-ethoxycarbonyl-1-phenyl-5H-1,2,4-triazolo[4,5-a] pyrimidin-5-ones 3a–e

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Time (min)</th>
<th>Yield (%)¹</th>
<th>IR bands (cm⁻¹)</th>
<th>'H NMR</th>
<th>Mp (°C)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C=O</td>
<td>CO₂Et</td>
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<tr>
<td>3a</td>
<td>Me</td>
<td>Me</td>
<td>10</td>
<td>83</td>
<td>1683 (s)</td>
<td>1720 (s)</td>
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<td></td>
<td>1.40 (t, 3 H, J = 7.1 Hz, CH₃CH₂), 2.50 (s, 3 H, CH₃), 2.90 (s, 3 H, CH₃), 4.39 (q, 2 H, J = 7.1 Hz, C₅H₄O), 7.50–8.20 (m, 5 H, Ar)</td>
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<tr>
<td>3b</td>
<td>Me</td>
<td>Et</td>
<td>11</td>
<td>80</td>
<td>1686 (m)</td>
<td>1722 (s)</td>
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<td>1.27 (t, 3 H, J = 7.9 Hz, CH₃CH₂), 1.39 (t, 3 H, J = 7.1 Hz, CH₃CH₂O), 2.52 (s, 3 H, CH₃), 3.40 (q, 2 H, J = 7.1 Hz, OCH₂), 4.39 (q, 2 H, J = 7.9 Hz, CH₃CH₂), 7.30–8.16 (m, 5 H, Ar)</td>
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<tr>
<td>3c</td>
<td>Et</td>
<td>Me</td>
<td>9</td>
<td>88</td>
<td>1688 (m)</td>
<td>1723 (s)</td>
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<td>1.29 (t, 3 H, J = 7.9 Hz, CH₃CH₂), 1.40 (t, 3 H, J = 7.1 Hz, CH₃CH₂O), 2.80 (q, 2 H, J = 7.1 Hz, OCH₂), 2.90 (s, 3 H, CH₃), 4.42 (q, 2 H, J = 7.9 Hz, CH₃CH₂), 7.51–8.15 (m, 5 H, Ar)</td>
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<tr>
<td>3d</td>
<td>Et</td>
<td>Et</td>
<td>12</td>
<td>84</td>
<td>1690 (m)</td>
<td>1720 (s)</td>
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<td>1.27–1.41 (m, 9 H, CH₃), 2.21 (q, 2 H, J = 7.2 Hz, OCH₂), 3.40 (q, 2 H, J = 7.8 Hz, CH₃CH₂), 4.39 (q, 2 H, J = 7.9 Hz, CH₃CH₂), 7.32–8.16 (m, 5 H, Ar)</td>
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<tr>
<td>3e</td>
<td>Me</td>
<td>PhCH₂</td>
<td>10</td>
<td>86</td>
<td>1690 (m)</td>
<td>1725 (s)</td>
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<td>1.40 (t, 3 H, J = 7.1 Hz, CH₃CH₂), 2.51 (s, 3 H, CH₃), 3.89 (s, 2 H, CH₂Ph), 4.40 (q, 2 H, J = 7.1 Hz, CH₂CH₃), 7.24–8.16 (m, 10 H, Ar)</td>
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¹ Elemental analysis: C ± 0.07, H ± 0.06, N ± 0.10.

References