Microwave-induced acetoacetylation of isoxazolyl amines with β-keto esters

E Rajanarendrer*, K Ramu & D Karumkar
Department of Chemistry, Kakatiya University
Warangal 506 009, India
E-mail: eligeti_rajan@yahoo.co.in
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The reaction of isoxazolyl amines with different β-keto esters under microwave irradiation, without using any catalyst and/or solvent leads to the formation of isoxazolyl amide derivatives by acetoacetylation.

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The interaction of hetaryl amines with 1,3-difunctional compounds e.g. β-keto esters, malononitriles in the presence of acid catalyst is a commonly employed reaction for preparation of enamines, which are then cyclized to the desired products 1,2. Keeping in view the potential of microwave technology in organic synthesis 3,4, and as a sequel to our work on isoxazoles 5,6, we intend to carry out condensation of isoxazolyl amines with β-keto esters and malononitriles, for developing new heterocycles, under microwave irradiation. Instead of condensation of amine with ketone carbonyl group, it underwent acetoacetylation. Acetoacetylation of isoxazolyl amines with different β-keto esters under microwave irradiation without any catalyst and/or solvent is reported.

The reaction of 4-amino-3-methyl-5-styryl isoxazole 10 obtained from the corresponding 3-methyl-4-nitro-5-styrylisoxazole 11 with β-keto esters viz., ethyl acetoacetate, trifluoroethyl acetoacetate, ethyl benzoyl acetate, 2-carboethoxy cyclohexanone, 2-carboethoxy cyclopentanone and with malonic ester separately was conducted in the absence of any catalyst and/or solvent under microwave irradiation. To our surprise, the amines 1 were acetoacetylated to the corresponding amide derivatives without even trace formation of enamine, just in 5-15 min. The course of the reaction occurred in such a way that the amine made nucleophilic attack on ester group of different β-keto esters in preference to the ketone carbonyl group and eliminated ethoxy group to result in the formation of amide derivatives by unexpected N-acetoacetylation (Scheme I). Similar results have been observed in the case of diethyl malonate. N-(3-methyl-5-styryl-isoxazol-4-yI)-3-oxobutanamide 2 formed by reaction of isoxazolyl amine with ethyl acetoacetate showed two carbonyl frequencies at 1700
and 1680 cm⁻¹ indicating the absence of ester carbonyl. ¹H NMR spectrum of 2a did not show the signals due to ethyl group, rather it showed three independent singlets at δ 1.8 and 2.2 due to two methyl group protons and methylene protons appeared as a sharp singlet at δ 3.9. NH proton of amide moiety exhibited a broad singlet at δ 9.5, which is D₂O exchangeable. The mass spectrum confirmed the product formation by showing a molecular ion at m/z 284.

To determine scope of this reaction, another isoxazolyl amine viz., 3-amino-5-methylisoxazole was reacted with different β-keto esters as well as with malonic ester separately under microwave irradiation. Once again, in the present process, the amine reacted with ester carbonyl group to give unexpected N-acetoacetylated product viz., N-(3-methyl-5-isoxazoloyl)-3-oxobutanamide 4 (Scheme I).

The new products have been characterized by elemental analysis and spectral data, which are well in agreement with the proposed structures. In the present investigation, we have utilised six different β-keto esters to study the generality of the reaction. In all the cases, the N-acetoacetylation occurred in preference to the condensation and ended up with high yields of the products (Table 1).

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Time (min)</th>
<th>Mol. formula</th>
<th>Found (%) Calcd</th>
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<tr>
<td>2a</td>
<td>CH₂COCH₃</td>
<td>90</td>
<td>90</td>
<td>6</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>67.57 5.65 9.79</td>
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<tr>
<td>2b</td>
<td>CH₂COF₃</td>
<td>154</td>
<td>95</td>
<td>6</td>
<td>C₁₆H₁₆N₂O₃F₂</td>
<td>(67.60 5.63 9.85)</td>
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<tr>
<td>2c</td>
<td>CH₂COPh</td>
<td>162</td>
<td>92</td>
<td>8</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>72.81 5.20 8.10</td>
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<tr>
<td>2d</td>
<td></td>
<td>142</td>
<td>95</td>
<td>7</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>(72.83 5.20 8.09)</td>
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<tr>
<td>2e</td>
<td></td>
<td>130</td>
<td>95</td>
<td>5</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>69.66 5.82 9.03</td>
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<tr>
<td>2f</td>
<td>CH₂CO₂C₂H₅</td>
<td>110</td>
<td>90</td>
<td>15</td>
<td>C₁₆H₁₆N₂O₄</td>
<td>(69.67 5.80 9.03)</td>
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<tr>
<td>4a</td>
<td>CH₂COCH₃</td>
<td>115</td>
<td>90</td>
<td>8</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>(64.96 5.73 8.91)</td>
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<tr>
<td>4b</td>
<td>CH₂COF₃</td>
<td>140</td>
<td>95</td>
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<td>C₁₆H₁₆N₂O₃F₂</td>
<td>(52.74 5.49 15.38)</td>
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<td>-CH₂COPh</td>
<td>170</td>
<td>95</td>
<td>10</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>(63.95 4.88 11.48)</td>
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<tr>
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<td></td>
<td>161</td>
<td>95</td>
<td>9</td>
<td>C₁₆H₁₆N₂O₃</td>
<td>(63.93 4.91 11.47)</td>
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<td>6</td>
<td>C₁₆H₁₆N₂O₃</td>
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<td>90</td>
<td>20</td>
<td>C₁₆H₁₆N₂O₄</td>
<td>(57.69 5.76 13.46)</td>
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</table>
In summary, we have developed a protocol for acetoacetylation of -NH₂ function using different β-keto esters under microwave irradiation. The reaction has general applicability, as it is extendable to a variety of β-keto esters as well as to aryl and heteraryl amines and has synthetic utility in organic chemistry by acting as a good synthon for further reactions. To the best of our knowledge, this happens to be first report on the N-acetoacetylation of five membered heterocycle.

**Experimental Section**

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrometer; ¹H NMR spectra on a Varian Gemini 200 MHz spectrometer using tetramethyl silane as internal standard; and mass spectra on a Jeol JMC D-300 spectrometer. A domestic microwave oven (LG-MS 257 PL) at 2450 MHz (900 Watts) was used in all experiments.

**General procedure for the preparation of N-(3-methyl-5-styryl-isoxazol-4-yl)-3-oxobutanamidine 2.**

A mixture of 4-amino-3-methyl-5-styrylisoxazole (0.01 mole) and ethyl acetoacetate (0.02 mole) was taken into conical flask and capped with a glass funnel and irradiated at 540 watts for 5-15 min. The gummy product obtained was triturated with pet. ether and filtered with cold methanol. Recrystallization was effected from ethanol.

**2a:** IR (KBr): 1627 (NHCO), 1705 (C=O), 3100 (NH) cm⁻¹; ¹H NMR (CDCl₃): 6 1.8 (s, 3H, CH₃), 2.2 (s, 3H, CH₂), 3.9 (s, 2H, CH₂), 6.8 (d, 1H, -CH=CH₂), 7.2 - 7.6 (m, 6H, Ar-H and -CH=CH₂), 9.5 (bs, 1H, NH, D₂O exchangeable); MS: m/z 284 (M⁺), 131 (base peak = Ph-CH=CH-CO⁻).

**2c:** IR (KBr): 1685 (NHCO), 1710 (C=O), 3400 (NH) cm⁻¹; ¹H NMR (CDCl₃): 6 2.3 (s, 3H, CH₃), 4.0 (s, 2H, CH₂), 6.8 (d, 1H, CH=CH₂), 7.0 - 7.5 (m, 11H, Ar-H and -CH=CH₂), 9.8 (bs, 1H, NH, D₂O exchangeable); MS: m/z 346 (M⁺).

**2f:** IR (KBr): 1685 (NHCO), 1735 (C=O ester), 3342 (NH) cm⁻¹; ¹H NMR (CDCl₃): 6 1.4 (t, 3H, CH₂CH₃), 2.2 (s, 3H, isoxazole CH₃), 3.4 (s, 2H, COCH₂CO₂Et), 4.3 (q, 2H, CH₂CH₃), 6.8 (d, 1H, -CH=CH₂), 7.2-7.6 (m, 6H, Ar-H and -CH=CH₂), 8.8 (s, 1H, NH, D₂O exchangeable); MS: m/z 314 (M⁺).

**General procedure for the preparation of N-(3-methyl-5-isoxazolyl)-3-oxobutanamidine 4.** A mixture of 5-amino-3-methyl-isoxazole (0.01 mole) and ethyl acetoacetate (0.02 mole) was taken in Borosil conical flask and capped with a glass funnel and irradiated at 540 watts for 6-20 min. The gummy product obtained was triturated with pet ether and filtered with cold methanol and recrystallization was effected from ethanol.

**4a:** IR (KBr): 1690 (NHCO), 1700 (C=O), 3225 (NH) cm⁻¹; ¹H NMR (CDCl₃): 6 2.3 (s, 3H, isoxazole CH₃), 2.5 (s, 3H, COCH₂), 3.8 (s, 2H, CH₂), 6.6 (s, 1H, isoxazole-H), 10.5 (s, 1H, NH, D₂O exchangeable); MS: m/z 182.

**4c:** IR (KBr): 1680 (NHCO), 1705 (C=O), 3300 (NH) cm⁻¹; ¹H NMR (CDCl₃): 6 2.4 (s, 3H, CH₃), 4.2 (s, 2H, CH₂), 6.7 (s, 1H, isoxazole-H), 7.2-8.0 (m, 5H, Ar-H).

**4f:** IR (KBr): 1700 (NHCO), 1745 (CO₂C₂H₅), 3380 (NH) cm⁻¹; ¹H NMR (CDCl₃): 6 1.3 (t, 3H, CH₂CH₃), 2.4 (s, 3H, isoxazole-CH₁), 3.5 (s, 2H, COCH₂CO₂Et), 4.2 (q, 2H, CH₂CH₃), 6.6 (s, 1H, isoxazole-H), 9.8 (s, 1H, NH, D₂O exchangeable); MS: m/z 212 (M⁺).

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**References**