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LETTERS TO THE EDITOR

Synthesis of 5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one in Supercritical Carbon Dioxide

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Abstract—5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one, an intermediate product in the synthesis of the antiviral drug Triazid®, was obtained for the first time by condensation of 3*H*-1,2,4-triazol-5-amine with ethyl acetoacetate in the presence of a catalytic amount of $ZnCl_2$ in supercritical carbon dioxide (200 bar) under solvent-free conditions. Depending on the temperature and reaction time, the conversion was 90%.

Keywords: 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one, supercritical carbon dioxide, solvent-free synthesis

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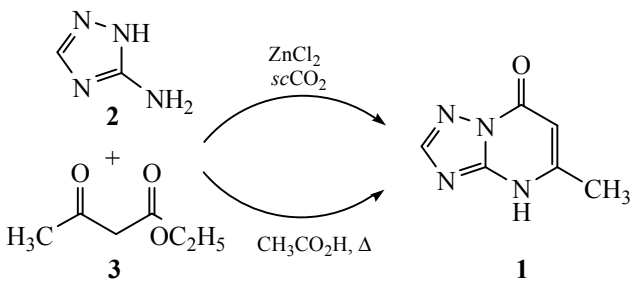
Development of pharmaceutical industry is closely related to the problem of disposal of large amounts of industrial wastes [1]. Implementation of the "green chemistry" principles provides favorable conditions for the solution of this problem. For example, the use of large amounts of organic solvents in industrial processes creates a high environmental hazard [2]. Therefore, replacement of organic solvents by supercritical fluids that are non-flammable, low toxic, and chemically inert, e.g., by carbon dioxide, may be environmentally benign [3].

Herein, we report the first synthesis of 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (**1**), an intermediate product in the preparation of the antiviral drug Triazid® [4], in supercritical carbon dioxide. The synthesis of **1** in up to 83% yield by cyclocondensation of 3*H*-1,2,4-triazol-5-amine (**2**) with ethyl acetoacetate (**3**) (Scheme 1) in boiling acetic acid was described in [5, 6]. We believed it reasonable to replace acetic acid by a Lewis acid such as zinc(II) chloride and to use supercritical carbon dioxide (200 bar) to dissolve all the reactants. The reaction conditions were optimized by varying the reaction temperature and time. The results are given in the table.

Obviously, increase of the reaction temperature or time increases the yield. However, unlike the conventional procedure, we have synthesized compound **1** in a higher yield, which indicates that carrying out the reaction in supercritical carbon dioxide is more advantageous.

Thus, we were the first to demonstrate that 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one can

Scheme 1.



Synthesis of 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (**1**) in supercritical carbon dioxide in the presence of $ZnCl_2$

Reaction time, min	Yield,[a] %		
	110°C	150°C	190°C
60	44	60	75 (69)
180	–	90 (85)	–

[a] Determined by HPLC according to the procedure described in [7]; the isolated yields are given in parentheses.

be synthesized in supercritical carbon dioxide in the presence of zinc(II) chloride. The effects of temperature and reaction time on the product yield were shown. The proposed procedure is advantageous since it does not require the use of organic solvents but ensures a comparable yield.

The synthesis was performed under microwave irradiation in a Waters TI-ReacSyS-250-200 supercritical fluid laboratory setup with a working pressure of 200 bar.

5-Methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (1). A mixture of aminotriazole **2** (42 mg, 0.5 mmol), ethyl acetoacetate (**3**, 73 mg, 0.56 mmol), and $ZnCl_2$ (7 mg, 0.05 mmol) in supercritical carbon dioxide was kept under the conditions indicated in Table 1. The mixture was analyzed by HPLC according to the procedure described in [7]. To isolate the product, the mixture was cooled to room temperature, and the precipitate was filtered off, washed with 40% aqueous ethanol, and dried. All physicochemical characteristics of the product were consistent with those reported in [5, 6].

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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