

Short Note

Methyl 6-Methyl-1-(4-methylphenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

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Abstract: Methyl 6-methyl-1-(4-methylphenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate has been synthesized *via* the modified Biginelli reaction from benzaldehyde, *p*-tolylurea, and methyl acetoacetate, promoted with microwave irradiation and catalyzed by TsOH under solvent-free conditions in high yield.

Keywords: dihydropyrimidinones; Biginelli reaction; microwave irradiation; solvent-free conditions

Recently, dihydropyrimidinones (DHPMs) and their derivatives have draw intensive interest because of their biological and pharmaceutical properties [1,2]. So, the synthesis of DHPMs has been revalued. The classical synthesis of dihydropyrimidinone was the Biginelli reaction of aldehyde, ethyl acetoacetate, and urea under acidic conditions [3]. In the last few decades, many improvements and modifications have been developed, including microwave promotion [4–6], ultrasound irradiation [7,8], ionic liquids [9–11] and the use of Lewis acid catalysts, such as NbCl₅/QN-NH₂ [12], BF₃ OEt₂/CuCl [13], formic acid [14], Yb(OTf)₃ [15], InCl₃ [16], NH₄Cl [17], Cu(OTf)₂ [18], Cu(ClO₄)₂ 6H₂O [19], *etc.*

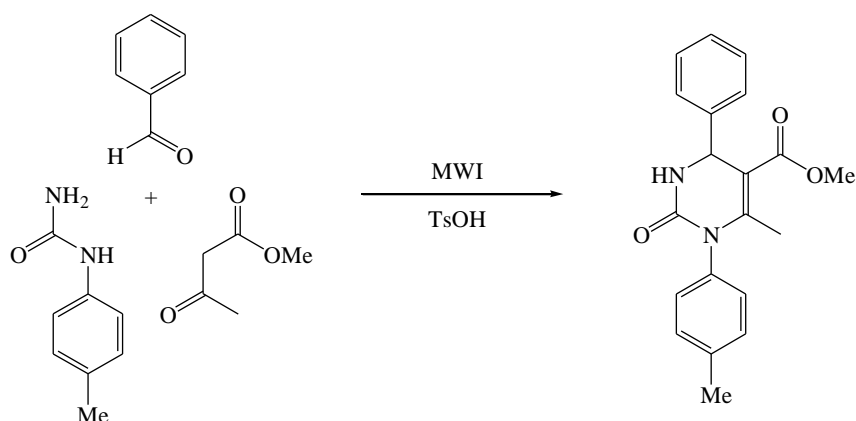
Chiral DHPMs *via* Biginelli condensation reaction have been realized [20–37].

A variety of substituents including *N*-substituted urea [38] and β-acylpyruvates [39] in the components have been investigated to produce differently substituted DHPMs for searching for DHPMs with distinguished biological and medicinal activities.

Microwave-assisted chemistry [40–42] and solvent-free reactions [42,43] have received a considerable attention. Application of microwave irradiation in organic synthesis is becoming an increasingly popular technology because of its rapid reaction rates, cleaner reaction conditions and ease of manipulation [43–51].

Herein, we report the synthesis of methyl 6-methyl-1-(4-methylphenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate from benzaldehyde, methyl acetoacetate, and *p*-tolylurea via the modified Biginelli reaction promoted with microwave irradiation and catalyzed by *p*-toluenesulfonic acid (TsOH) under solvent-free conditions in high yield (Scheme 1). This procedure had the advantages of short reaction time, simple and easy work-up, and it is environmentally benign. The product has been characterized by NMR (^1H and ^{13}C), IR, MS, and elemental analysis.

Scheme 1. The synthesis of the title compound *via* the modified Biginelli reaction.



Experimental Procedure

Benzaldehyde (2 mmol), methyl acetoacetate (3.6 mmol), *p*-tolylurea (2 mmol) and TsOH (anhydrous, 5% of aldehyde based) were irradiated in a microwave reactor (600 W) at 60 °C for 15 min and monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice with stirring and was filtrated, washed with ethanol (95%) to obtain the crude product. Recrystallization from ethanol afforded the pure target compound as white crystals, 0.59 g, yield of 87.7%, m.p. 159.5–162 °C.

Accordingly, our investigation showed that the best results were observed when the molar ratio of aldehyde, *p*-tolylurea and methyl acetoacetate was 1:1:1.8. Different catalysts including HCl, H₂SO₄, H₃PO₄, formic acid, acetic acid, TsOH, tartaric acid and iodine had been tested and it was found that TsOH was the best and that the yields were not obviously affected by the concentration of TsOH.

In summary, methyl 6-methyl-1-(4-methylphenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate has been synthesized from benzaldehyde, methyl acetoacetate, and *p*-tolylurea catalyzed by TsOH and promoted with microwave irradiation under solvent-free conditions in high yield and characterized by NMR (^1H and ^{13}C) and IR spectra. The preparation is characteristic of short reaction time, simple and easy work-up, and it is environmentally benign. This protocol developed a facile and green synthesis of *N*-substituted 1,2,3,4-tetrahydropyrimidin-2-one and extended the utility of substituted urea in the venerable Biginelli reaction.

Structural Characterization

^1H NMR (Bruker 300 MHz, DMSO- d_6): δ_{H} 8.13 (br s, 1 H, N-H), 7.42–7.05 (m, 9 H, Ar-H), 5.26 (br s, 1 H, 4-CH), 3.58 (s, 3 H, OCH₃), 2.33 (s, 3 H, ArCH₃), 2.02 (s, 3 H, CH₃) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): δ_{C} 166.5, 152.7, 149.8, 144.4, 137.9, 135.6, 130.0, 129.9, 129.1, 128.0, 126.6, 103.9, 53.4, 51.6, 21.1, 18.5 ppm. IR (Bruker Tensor 27, KBr): ν_{max} 3472, 1694, 1211, 1076 cm^{-1} . HRMS (Bruker maXis, ESI): m/z 337.1535 ($[\text{M} + \text{H}]^+$), C₂₀H₂₀N₂O₃ required: 337.1547 (M + H). Anal. calcd. (PE2400 II CHONS): calcd. for C₂₀H₂₀N₂O₃: C 71.41, H 5.99, N 8.33; found: C 71.68, H 5.82, N 8.53.

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