

Short Note

Methyl 6-Methyl-4-(4-iodophenyl)-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidinecarboxylate

Ning Pan, Wenwen Zhang and Qingjian Liu *

Chemical Engineering and Materials Science, Engineering Research Center of Pesticide and Medicine Intermediate Clean Production, Ministry of Education, College of Chemistry, Shandong Normal University, Jinan 250014, China

* Author to whom correspondence should be addressed; E-Mail: liujq@sdnu.edu.cn.

Received: 23 October 2009 / Accepted: 11 December 2009 / Published: 15 December 2009

Abstract: Methyl 6-methyl-4-(4-iodophenyl)-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidine-carboxylate has been synthesized *via* Biginelli reaction of 4-iodobenzaldehyde, methyl acetoacetate and thiourea, promoted by microwave irradiation in the presence of iodine under solvent-free conditions in high yield and good purity.

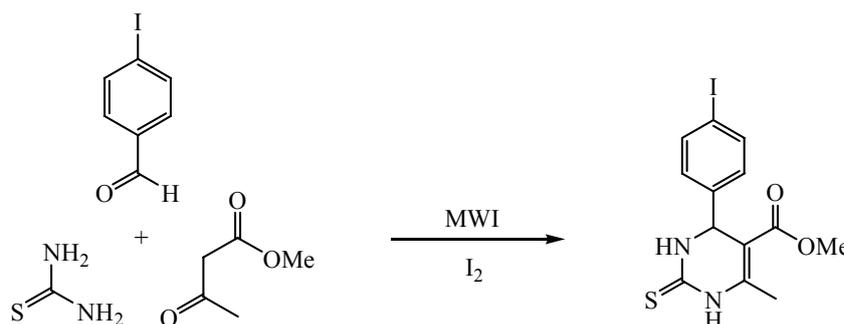
Keywords: Biginelli reaction; solvent-free conditions; microwave irradiation; 3,4-dihydropyrimidin-2(1*H*)-thione

In recent years, dihydropyrimidinones (DHPMs) and their derivatives have attracted considerable attention in natural and synthetic organic chemistry because of their biological and medicinal properties [1,2]. The venerable Biginelli reaction [3,4], one-pot cyclocondensation of aldehyde, β -ketoester, and urea or thiourea, is inarguably one of the most useful multi-component reactions. Polyfunctionalized dihydropyrimidines represent a heterocyclic system of remarkable pharmacological properties such as antiviral, antitumor, antibacterial, and antiinflammatory properties.

Because of global environmental concern and social sustainable development, green synthesis has received considerable attention [5]. Molecular iodine as an inexpensive, nontoxic, readily available catalyst has been used successfully in the Biginelli reaction [6,7], affording the corresponding products in excellent yields with high selectivity [6–9]. Microwave-assisted chemistry has also attracted a considerable attention in recent years and has been applied successfully in various fields of synthetic organic chemistry [10–13], including solvent-free reactions [12,13].

As our continuous investigation on the methodology of green synthesis, we report herein the synthesis of the new DHPM compound, methyl 6-methyl-4-(4-iodophenyl)-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidinecarboxylate *via* a Biginelli three-component cyclocondensation of 4-iodobenzaldehyde, methyl acetoacetate and thiourea, catalyzed with iodine and promoted by microwave irradiation (MWI) under solvent-free conditions (Scheme 1). The title compound has been fully characterized by NMR (^1H and ^{13}C), IR, MS, and elemental analysis. This protocol is proven to be efficient and environmentally benign.

Scheme 1.



Experimental Procedure

4-Iodobenzaldehyde (2.5 mmol), methyl acetoacetate (5 mmol), thiourea (5 mmol) and iodine (0.2 mmol) were mixed thoroughly and 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 ethyl acetate, cooled to precipitate out, and filtered off to obtain the crude product in high yield. Recrystallization from ethanol afforded the pure title compound as yellow crystals in a yield of 87.7%, m.p. 187.9–189.2 °C.

Moreover, our investigation showed that the best results were observed when the molar ratio of aldehyde, acetoacetate and thiourea was 1:2:2. In addition, it was found that the yields were not obviously affected by different amount of iodine.

^1H NMR (Bruker 300 MHz, DMSO-*d*₆): δ_{H} 10.38 (s, 1H, N-H), 9.66 (s, 1H, N-H), 7.71 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.01 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.11 (d, *J* = 3.0 Hz, 1H, C4-H), 3.54 (s, 3H, OCH₃), 2.29 (s, 3H, CH₃) ppm.

^{13}C NMR (75 MHz, DMSO-*d*₆): δ_{C} 174.8, 165.9, 146.0, 143.5, 137.9, 129.1, 100.5, 94.3, 54.0, 51.6, 17.7 ppm.

IR (Bruker Tensor 27, KBr): ν_{max} 3453, 2361, 1662, 1576, 1196, 1118 cm⁻¹.

MS (API 4000, ESI): *m/z* (%) 389.2 (M⁺, base peak).

Elemental anal. (Perkin Elmer PE 2400 II HONS): calcd for C₁₃H₁₃IN₂O₂S: C 40.21, H 3.37, N 7.20; found: C 40.22, H 3.38, N 7.22.

Acknowledgements

The authors are grateful to Liu Zhixian and Yu Lixin for determinations of NMR, IR and elemental analysis.

References

1. Kappe, C.O. 100 Years of Biginelli dihydropyrimidine synthesis. *Tetrahedron* **1993**, *49*, 6937–6963.
2. Kappe, C.O. Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. *Acc. Chem. Res.* **2000**, *33*, 879–888.
3. Biginelli, P. Aldehyde–urea derivatives of aceto- and oxaloacetic acids. *Gazz. Chim. Ital.* **1893**, *23*, 360–413.
4. Sanjeev, P.; Gokavi, G.S. Heteropoly acid catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. *Catal. Commun.* **2007**, *8*, 279–284.
5. Walsh, P.J.; Li, H.M.; de Parrodi, C.A. A green chemistry approach to asymmetric catalysis: solvent-free and highly concentrated reactions. *Chem. Rev.* **2007**, *107*, 2503–2545.
6. Saxena, I.; Borah, D.C.; Sarma, J.C. Three component condensations catalyzed by iodine–alumina for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation and solvent-free condition. *Tetrahedron Lett.* **2005**, *46*, 1159–1160.
7. Bhosale, R.S.; Bhosale, S.V.; Bhosale, S.V.; Wang, T.; Zubaidha, P.K. An efficient, high yield protocol for the one-pot synthesis of dihydropyrimidin-2(1*H*)-ones catalyzed by iodine. *Tetrahedron Lett.* **2004**, *45*, 9111–9113.
8. Ko, S.; Sastry, M.N.V.; Lin, C.; Yao, C.-F. Molecular iodine-catalyzed one-pot synthesis of 4-substituted-1,4-dihydropyridine derivatives via Hantzsch reaction. *Tetrahedron Lett.* **2005**, *46*, 5771–5774.
9. Srinivas, K.V.N.S.; Das, B. Iodine-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones: A simple and efficient procedure for the Biginelli reaction. *Synthesis* **2004**, *13*, 2091–2093.
10. de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A.; Langa, F. Cycloadditions under microwave irradiation conditions: Methods and applications. *Eur. J. Org. Chem.* **2000**, 3659–3673.
11. Varma, R.S. Solvent-free synthesis of heterocyclic compounds using microwaves. *J. Heterocycl. Chem.* **1999**, *36*, 1565–1571.
12. Varma, R.S. Solvent-free organic syntheses using supported reagents and microwave irradiation. *Green Chem.* **1999**, *1*, 43–55.
13. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. New solvent-free organic synthesis using focused microwaves. *Synthesis* **1998**, 1213–1234.