

Short Note

Dimethyl 1,4-Dihydro-2,6-dimethyl-1-(4-methylphenyl)-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate

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Abstract: Dimethyl 1,4-dihydro-2,6-dimethyl-1-(4-methylphenyl)-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate has been synthesized via Hantzsch condensation reaction of *p*-methoxybenzaldehyde, methyl acetoacetate and *p*-toluidine promoted by microwave irradiation (MWI) in the presence of iodine under solvent-free conditions.

Keywords: Hantzsch reaction; dimethyl 1,4-dihydro-2,6-dimethyl-1-(4-methylphenyl)-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate; microwave irradiation; solvent-free conditions

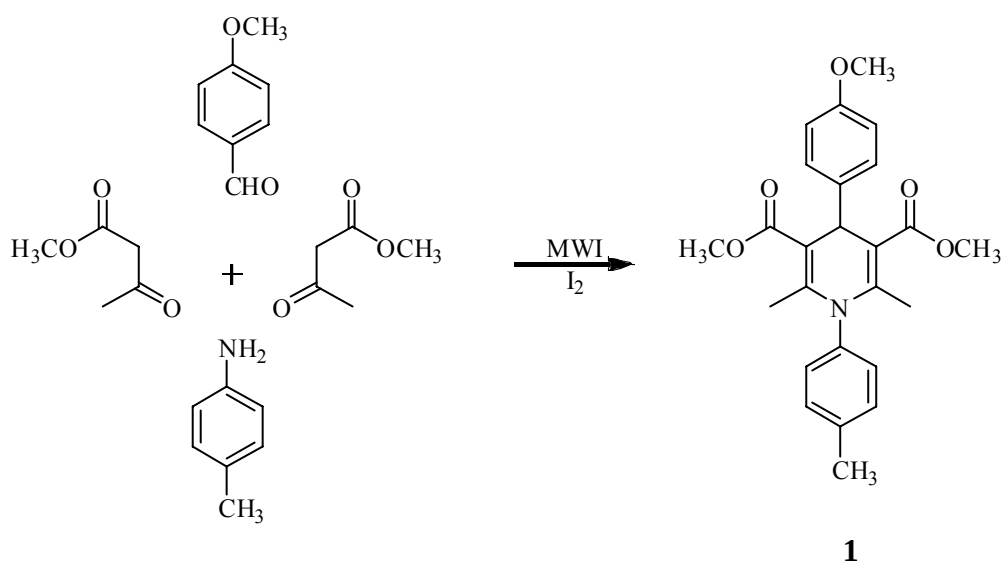
Hantzsch 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers [1], and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases [2] including hypertension [3]. Shah and co-workers have studied the role of 1,4-dihydropyridines as chemotherapeutic agents, such as multi-drug-resistance (mdr) reversal in tumor cells [4], potential immunomodulating [5] and antitubercular compounds as well [6,7]. In light of this, the further study of *N*-substituted DHP skeleton proved to be important for mdr reversal in tumor cells [8]. Thus, the synthesis of *N*-substituted 1,4-dihydropyridines is of considerable importance.

The most classical synthesis of symmetrical 1,4-DHPs is the three-component condensation of aryl aldehydes, ammonia, or amines and β -ketoesters, which was reported in 1882 by Hantzsch [9]. However, the yields of 1,4-DHPs obtained by the Hantzsch method are generally low. Modified synthetic methodologies [10–14] improved the yields but using expensive reagents and require longer reaction times. Thus, the development of an efficient and versatile method for the preparation of

Hantzsch 1,4-DHPs is an active ongoing research area. The eco-friendly goal of making organic compounds without using solvents has come several steps closer in recent years [15]. And the microwave activation stands among the alternative routes proposed during the past decade due to the drastic reduction of reaction times [16–18]. Recently, the synthesis of organic compounds assisted by microwaves [19] under solvent free conditions [20,21], is an improved technique. Due to greater selectivity, rapid transfer of energy, significant practical simplicity and pure products, microwave-assisted reactions have greater advantages over conventional homogeneous methods. In recent times, the use of molecular iodine [22–25] has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a good catalyst for various organic synthesis [26–28].

Herein, we report the synthesis of dimethyl 1,4-dihydro-2,6-dimethyl-1-(4-methylphenyl)-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate **1** via Hantzsch condensation reaction of *p*-methoxybenzaldehyde, methyl acetoacetate and *p*-toluidine promoted by microwave irradiation (MWI) in the presence of iodine 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

A mixture of *p*-methoxybenzaldehyde (0.68 g, 5 mmol), methyl acetoacetate (1.39 g, 12 mmol), *p*-toluidine (0.54 g, 5 mmol) with a catalytic amount of iodine was irradiated in a microwave reactor (800 W) for 15 min at 80 °C. After completion of the reaction as indicated by TLC, the crude product was purified by flash column chromatography on silica gel (300–400 mesh) and eluted with ethyl acetate-petroleum ether (1:12) to afford the title compound **1** as white crystals, 1.75 g, yield 83.2%, m.p. 153–155 °C.

Moreover, our investigation showed that the best results were obtained when the molar ratio of aldehyde, acetoacetate and *p*-toluidine was 1:2.4:1. In addition, the best yield is achieved when the amount of iodine is 3% based on the substrate.

Structural Characterization

^1H NMR (Bruker 300 MHz, CDCl_3): δ_{H} 7.26 (d, $J = 8.4$ Hz, 2 H, Ar-H), 7.22 (d, $J = 7.8$ Hz, 2H, Ar-H), 6.98 (d, $J = 7.8$ Hz, 2 H, Ar-H), 6.83 (d, $J = 8.4$ Hz, 2 H, Ar-H), 5.07 (s, 1 H, CH), 3.78 (s, 3 H, OCH_3), 3.68 (s, 6 H, 2^*OCH_3), 2.40 (s, 3 H, PhCH_3), 2.05 (s, 6 H, 2^*CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 168.56, 158.06, 147.67, 139.27, 138.66, 137.71, 129.95, 128.17, 113.57, 105.67, 55.14, 51.14, 37.59, 21.09, 18.55 ppm. IR (Bruker Tensor 27, KBr): 3392, 2951, 1677, 727 cm^{-1} . MS (AGILENT 5973N MSD, EI): m/z 422.6 ($\text{M}^+ + 1$). Elemental Anal. (Perkin Elmer PE 2400 II HONS): calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_5$ (421.49): C, 71.24; H, 6.46; N, 3.32; O, 18.98. Found: C, 71.3; H, 6.3; N, 3.4; O, 18.8.

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