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Short Note

4-(3,5-Dibromo-4-hydroxyphenyl)-3-butoxycarbonyl-5-ethoxycarbonyl-2-methyl-6-phenyl-1,4-dihydropyridine

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Abstract: One-pot two-step Hantzsch synthesis of 4-(3,5-dibromo-4-hydroxyphenyl)-3-butoxycarbonyl-5-ethoxycarbonyl-2-methyl-6-phenyl-1,4-dihydropyridine under solvent- and catalyst-free conditions promoted with microwave irradiation is presented.

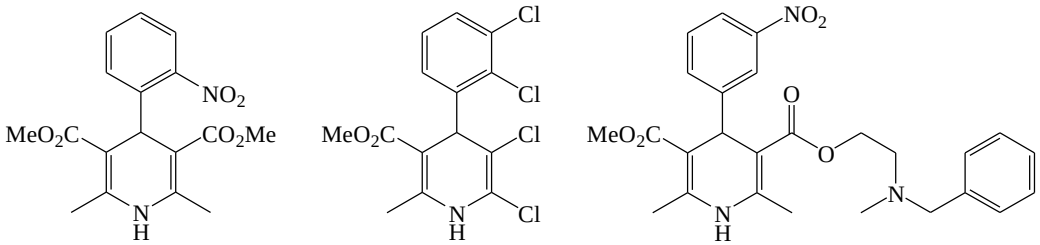
Keywords: 1,4-Dihydropyridines; Hantzsch reaction; microwave irradiation; solvent- and catalyst-free conditions

1,4-Dihydropyridines (DHPs) have attracted immense attention for synthetic and medicinal chemists due to their biological and pharmacological properties [1]. 1,4-DHPs, as a class of calcium modulators, are extensively investigated because of their pharmacological activity as drugs in vasodilatation, hepatoprotection, neuromodulatory, cognition, memory enhancing, neuroprotection, anti-atherosclerosis, anti-diabetes, antioxidant, anti-mutagenic, and anti-tumor [2]. The most notable examples are the 1,4-DHP based calcium channel blocker drugs such as nifedipine, felodipine, and nicardipine (Figure 1), which are widely used for the treatment of hypertension and related cardiovascular diseases [3,4].

In order to model and understand these biological properties and to develop new chemotherapeutic agents based upon the 1,4-DHP motif, considerable effort has been devoted to establish efficient and practical formation methods. The classical synthesis of symmetrical 1,4-DHPs is the three-component one-pot Hantzsch condensation reaction of aldehydes, β-ketoesters, and ammonia or amines [5]. Many improvements and modifications have been developed, including the use of ionic liquids [6], high

temperatures at reflux [7] and catalysts such as boronic acids [8], metal triflates [9], molecular iodine [10], TMS iodide [11], Bu_4NHSO_4 [12], bakers' yeast [13], ceric ammonium nitrate [14], HCl generated *in situ* [15], and silica-supported acids [16]. Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as longer reaction times, unsatisfactory yields, high costs, harsh reaction conditions, and the use of a large quantity of volatile organic solvents.

Figure 1. 1,4-DHP drugs for cardiovascular diseases.

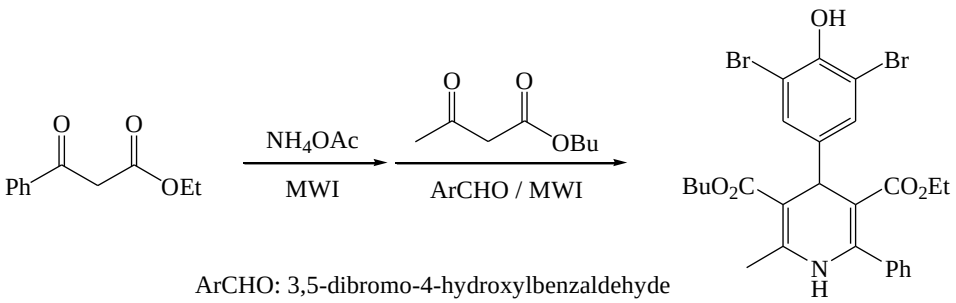


Nifedipine Felodipine Nicardipine

The synthesis of bioactive molecules should preferably be facile, fast, and efficient with minimal workup [17]. Microwave irradiation is an extremely powerful tool for reducing reaction time and increasing desired product yields [18,19]. Unsymmetrical 1,4-DHPs represent effective drug moieties (Felodipine 3, for example) and sometimes possess even better pharmacological activities [20-22].

Herein, we reported a one-pot two-step Hantzsch synthesis of 4-(3,5-dibromo-4-hydroxyphenyl)-3-butoxycarbonyl-5-ethoxycarbonyl-2-methyl-6-phenyl-1,4-dihydropyridine under solvent- and catalyst-free conditions promoted with microwave irradiation, as shown in Scheme 1. The title compound has been fully characterized by NMR (^{1}H and ^{13}C), IR, MS, and elemental analysis. This protocol is proven to be facile, efficient, practical, and environmentally benign.

Scheme 1. Synthesis of the title compound 1.



ArCHO: 3,5-dibromo-4-hydroxylbenzaldehyde

Experimental

A mixture of ethyl benzoylacetate (0.96 g, 5 mmol) and ammonium acetate (0.77 g, 10 mmol) was heated at 75 ℃ for 15 min under microwave irradiation (600 W). Then, butyl acetoacetate (0.79 g, 5 mmol) and 3,5-dibromo-4-hydroxybenzaldehyde (1.40 g, 5 mmol) were added, and the mixture was heated at 75 ℃ for 15 min under microwave irradiation (600 W). After completion of the reaction as monitored by TLC, the crude mixture was purified by flash column chromatography on silica gel

(300–400 mesh) eluted with ethyl acetate-petroleum ether (1:7, v/v) to afford the pure product **1** as pale yellow crystals, 2.36 g, 80% yield, mp 184–185 ℃.

Structural Characterization

^{1}H NMR (Bruker 300 MHz, DMSO-d_6): δ_H 9.74 (br. s, 1 H, NH), 9.18 (s, 1 H, OH), 7.38 (m, 7 H, Ar-H), 4.82 (s, 1 H, CH), 4.05 (q, 2 H, *J* = 6.2 Hz, O*CH*$_2$CH$_3$), 3.70 (q, 2 H, *J* = 7.1 Hz, O*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.31 (s, 3 H, CH$_3$), 1.53 (m, 2 H, *J* = 7.6 Hz, OCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.27 (m, 2 H, *J* = 7.5 Hz, OCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.87 (t, 3 H, *J* = 7.3 Hz, OCH$_2$*CH*$_3$), 0.71 (t, 3 H, *J* = 7.0 Hz, OCH$_2$CH$_2$CH$_2$*CH*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.2, 166.6, 147.8, 145.8, 144.6, 142.4, 136.5, 131.6, 129.3, 129.0, 128.4, 128.0, 109.4, 104.1, 103.1, 64.0, 59.8, 39.1, 30.8, 19.6, 19.4, 13.8, 13.6 ppm. IR: υ_{max} 3290, 1679, 1475, 1213, 789, 697 cm^{-1}. MS (AGILENT 5973N MSD, EI): m/z 593.2 (M^+). Elemental anal. (Perkin Elmer PE 2400 II HONS): calcd for $C_{26}H_{27}Br_2NO_5$ (593.30): C, 52.63; H, 4.59; N, 2.36. Found: C, 52.75; H, 4.53; N, 2.30.

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