Synthesis and optimization of methyl 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(substituent benzylidene)pyridine-3-carboxylate

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1. Introduction

Dihydropyridine derivatives have been used as a calcium antagonist [1-2] to treat hypertension; they elicit their therapeutic effects by reversibly blocking Ca2+ influx through L-type calcium channels (LCCs Ca.1) found in cardiac and vascular smooth muscle.

Method of the one-pot synthesis of dihydropyridine derivatives has been reported [3-6]. In those reports, the aromatic aldehyde and dicarbonyl compounds and ammonium acetate was added into a flask in the ratio of 1:2:1, respectively. After being refluxed for some hours in ethanol, symmetric 1,4-dihydro-Hantzsch Pyridine derivatives were obtained, it was easy to operate, but the reaction time was long, and the final treatment was complicated, symmetrical dihydropyridine derivatives were obtained as shown Figure 1.

![Figure 1. Preparation of the symmetrical dihydropyridine derivatives.](image)

While the dihydropyridine derivatives could not be obtained through this method. In this paper, methyl 3-aminobut-2-enoate was first produced by reacting methyl acetacetate with ammonia and benzyl compounds were synthesized from the substituted benzaldehyde and pentane-2,4-dione, then the target product was synthesized through Michael addition reaction between methyl 3-aminobut-2-enoate and benzyl compounds (Figure 2).

As antihypertensive drugs, unsymmetrical molecular structure [7] showed good pharmacological effects. Due to their important pharmacological activities, the synthesis of Hantzsch dihydropyridine derivatives molecules is of great significance to treat cerebrovascular diseases.

![Figure 2. Preparation of the unsymmetrical dihydropyridine derivatives.](image)

2. Experimental

All chemicals and solvents were obtained from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, P.R. China). The yields refer to analytically pure compounds and were not optimized. Melting points were taken on an X4-digital melting point reader and were uncorrected. 1H NMR spectra were recorded respectively with a Varian BRUKER 400 spectrometer using TMS as an internal standard in CDCl3. IR spectra were recorded on a Nexus-470 IR spectrometer, using KBr pellets. Elemental
analyses were performed in a CE-440 instrument. MS data was recorded by Agilent 6890N-5973 GC-MS.

2.1. Methyl 3-aminobut-2-enoate (I)

25% ammonia (26.9 mL, 0.36 mol) were added to a three-necked flask containing methyl acetocacetate (32.4 mL, 0.3 mol), and stirred for 2 h under ice cooling. White crystals formed giving 9.57 g (83.2%) of I, melting point: 84–85 °C (Literature [6], 85-86 °C), elemental analysis and IR spectra were in conformity with literature data.

2.2. 3-(3-nitrobenzylidene)pentane-2,4-dione (IIa)

Redistilled pentane-2,4-dione (5.2 mL, 0.05 mol) and acetic anhydride (5 mL, 0.05 mol) were added in a three-necked flask fitted with a stirrer, followed by dropwise addition of 1 mL of conc. sulfuric acid with stirring under ice-bath. Then, m-nitrobenzaldehyde (7.6 g, 0.05 mol) was added and stirred for 2 h after the solid was dissolved at room temperature, and further keep at 0 °C for 1 h. White crystals formed, then washed it with 10 mL of water and 95% ethanol for three times respectively. The product was purified by recrystallization from ethanol, and large white needle crystal of IIa (10.7 g), with a yield of 92.2% was obtained. 3-(3-nitrobenzylidene)pentane-2,4-dione (IIa): FT-IR (KBr, cm⁻¹): 3045 (υ-C=O), 1717 (υ-C=O), 1687 (υ-C=O), 1653 (υ-C=C), 1541 (υ(NO2)), 1319 (υ(NO2)). 1H NMR (400 MHz, CDCl3, δ, ppm): 2.219 (s, 3H, CO-CH3), 2.342 (s, 3H, CH3), 3.724 (s, 3H, COOCH3), 5.180 (s, 1H, CH), 5.262 (s, 1H, NH), 7.414-8.095 (m, 4H, ArH). MS (m/z): 217 [M⁺]. Anal. Calcd. for C17H18N2O4: C, 61.81; H, 5.49; N, 8.48. Found: C, 63.51; H, 5.67; N, 8.29 %.

2.5. Methyl 5-acyetyl-4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3-carboxylate (IIIb)

Compound IIb (4.7 g, 0.021 mol) and compound I (2.3 g, 0.023 mol) were added to a three-necked flask containing 20 mL of dichloromethane as solvent, refluxed for 1 h under vigorous stirring, then vacuum distillated, a yellow solid appeared after dissolving in 20 mL of ethyl ether, recrystallized by toluene, the target product IIIb (5.53 g, 0.019 mol) with a yield of 90.1%, and the melting point, 191–193 °C was obtained. Methyl 5-acyetyl-4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethyl pyridine-3-carboxylate (IIIb): FT-IR (KBr, cm⁻¹): 3367 ν(N-H), 2995 ν(C-H), 1710 ν(C=O), 1664 ν(C=C), 1660 ν(C=O), 1580 ν(C=O)(ester), 1398, 1242, 1141. 1H NMR (500 MHz, CDCl3, δ, ppm): 2.717 (s, 3H, CH3), 2.509 (s, 3H, CH3), 3.773 (s, 3H, COOCH3), 5.439 (s, 1H, CH), 6.476 (s, 1H, NH), 7.079-7.411 (m, 4H, ArH), MS (m/z): 319[M⁺]. Anal. Calcd. for C17H18ClNO3: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.91; H, 5.77; N, 4.11 %.

3. Results and discussion

3.1. Methyl 3-aminobut-2-enoate (I)

Methyl 3-aminobut-2-enoate (I) was produced by reacting methyl acetocacetate with ammonia. The 83.2% yield is the highest when ammonia was used as the nitrogen source, because both of the reactants were liquid, the reaction time could be shortened to 2 h by solvent free reaction. Meanwhile, ammonia is easy to evaporate at higher temperature, so that the best reaction temperature is 0 °C in this process. Thus, the optimum route for this reaction is by using acetyl acetate with ammonia, with the ratio of 1:1.2 and under ice-bath for about 2 h (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Different conditions of the synthesis of compound I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The source of nitrogen</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Ammonium bicarbonate</td>
</tr>
<tr>
<td>Ammonia</td>
</tr>
<tr>
<td>Ammonium acetate</td>
</tr>
</tbody>
</table>

3.2. 3-(substituted-benzylidene) pentane-2,4-dione (II)

3-(substituted-benzylidene)pentane-2,4-dione (II) was produced from the substituted benzaldehyde and pentane-2,4-dione. Since the symmetric structure of pentane-2,4-dione cannot generate cis- and trans-isomers, pentane-2,4-dione was employed rather than the traditional ester [9-10] as the dicarbonyl compound, so the post-processing for (II) has been greatly simplified in our work. The middle product can be utilized directly in the next step without being purified by flash column chromatograph over silica. Various catalysts to produce compound II have been studied. The use of conc. sulfuric acid or piperidine acetate as catalysts have been reported [11]. But conc. sulfuric acid has greater side effects, produces more impurities and damages the environment. Piperidine acetate as the catalytic, the reaction was around 20 h [11], but through using H2SO4-acetic anhydride system rather than acetic acid-piperidine system, the reaction time can be shortened to 1.5 h under low temperature which effectively eliminates side reaction and the yield was higher than that at high temperature (Table 2).

3.3. Methyl 5-acyetyl-1,4-dihydro-2,6-dimethyl-4-(substituent benzylidene) pyridine-3-carboxylate (III)
Methyl 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(substituent benzylidene) pyridine-3-carboxylate was synthesized through Michael addition reaction between I and II. Formation of IIIa was indicated by the IR spectra; the bands at 3379 cm$^{-1}$ assigned to the N-H, 1722, 1695 cm$^{-1}$ assigned to the C=O group (on the dihydropyridine cycle) appeared; the formation of dihydropyridine cycle was confirmed from the broad band appearing in the $^1$H NMR spectrum at 5.180 (s, 1H, CH).

Characterizations of IIIb from IR and $^1$H NMR spectra were similar to IIIa.

**Table 2. Different conditions of synthesis of compound II.**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Temp., °C</th>
<th>Time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc. sulfuric acid</td>
<td>78</td>
<td>3.5</td>
<td>77.4 (a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>74.6 (b)</td>
</tr>
<tr>
<td>Piperidine acetate</td>
<td>78</td>
<td>3</td>
<td>81.2 (a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82.3 (b)</td>
</tr>
<tr>
<td>Piperidine acetate</td>
<td>25</td>
<td>22</td>
<td>86.1 (a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>91.8 (b)</td>
</tr>
<tr>
<td>Acetic anhydride-conc. sulfuric acid</td>
<td>0–5</td>
<td>1.5</td>
<td>92.0 (a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>92.2 (b)</td>
</tr>
</tbody>
</table>

Michael addition reaction occurred in this step, and the cyclization rate was very slow. The reactants were commonly refluxed in ethanol for tens of hours [12]. Here, the polar aprotic solvent dioxane instead of ethanol was used as the solvent in our work; the reaction time required was reduced to 15 h from 20 h [13] and the yield of IIIa, IIIb were 93.2% and 90.1%, respectively.

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**References**