European Journal of Chemistry 2 (3) (2011) 308-310

European Journal of Chemistry
Journal homepage: www.eurjchem.com

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

Rui Dong Liu and Jian Zhang*

*College of Chemistry and Materials, South-Central University for Nationalities, Wuhan, 430074, China*

**Corresponding author at: College of Chemistry and Materials, South-Central University for Nationalities, Wuhan, 430074, China. Tel.: +86.2762357762; fax: +86.2767842752. E-mail address: jianzhangye@gmail.com (J. Zhang).*

ARTICLE INFORMATION

Received: 27 May 2010
Received in revised form: 21 October 2010
Accepted: 28 October 2010
Online: 30 September 2011

KEYWORDS

Unsymmetrical
1, 4-dihydro-Hantzsch pyridine
Condensation
Catalyst
Cyclization
Polar aprotic solvent

ABSTRACT

Two 1,4-dihydro-Hantzsch pyridine derivatives were synthesized by three steps. In the condensation step, the reaction time can be shortened to 1.5 h through using $H_2SO_4$-acetic anhydride system as a catalyst rather than the acetic acid-piperidine systemin the cyclization step, the reaction time was shortened from 20 h in ethanol to 15 h in polar aprotic solvent, and the yield of two products also was increased from 43.3% and 39.7% in traditional solvent to 93.2% and 90.1% in polar aprotic solvent.

## 1. Introduction

Dihydropyridine derivatives have been used as a calcium antagonist [1-2] to treat hypertension; they elicit their therapeutic effects by reversibly blocking $Ca^{2+}$ influx through L-type calcium channels (LCCs $Ca_V1$) 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.

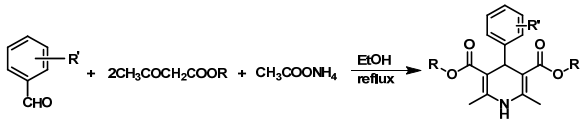


**Figure 1.** Preparation of the symmetrical dihydropyridine derivatives.

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 acetoacetate 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.

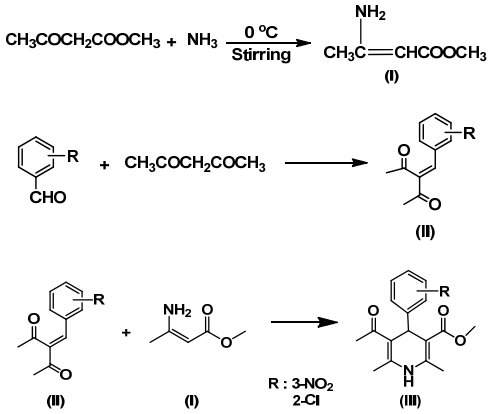


**Figure 2.** Preparation of the unsymmetrical dihydropyridine derivatives.

## 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 $CDCl_3$. IR spectra were recorded on a Nexus-470 IR spectrometer, using KBr pellets. Elemental


ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online) © 2011 EURJCHEM
DOI:10.5155/eurjchem.2.3.308-310.126

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 acetoacetate (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 [8], 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-nitrobenz ylidene)pentane-2,4-dione* (**IIa**): FT-IR (KBr, $cm^{-1}$): 3045 ν(C-H), 1717 ν(C=O), 1687 ν(C=O), 1653 ν(C=C), 1541 $\nu_{as}(NO_2)$, 1319 $\nu_s(NO_2)$. $^1H$ NMR (400 MHz, $CDCl_3$, δ, ppm): 2.159 (s, 3H, CO-$CH_3$), 2.499 (s, 3H, CO-$CH_3$), 7.303-7.429 (m, 4H, ArH), 7.768 (s, 1H, CH). Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.51; H, 4.09; N, 6.36 %.

### 2.3. 3-(2-chlorobenzylidene)pentane-2,4-dione (IIb)

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 1 mL of conc. sulfuric acid addition dropwise with stirring under ice-bath, then *o*-chlorobenzaldehyde (5.5 mL, 0.05 mol) was added, stirred for 0.5 h, then further stirred for 2 h under room temperature, washed to neutrality by 5% sodium carbonate solution and extracted by 10 mL ethyl acetate, the solvent was removed by vacuum distillation, yellow oily liquid of **IIb** was obtained with a yield of 87.5%. *3-(2-chlorobenzylidene)pentane-2,4-dione* (**IIb**): IR (KBr, $cm^{-1}$): 3027 ν(C-H), 1699 ν(C=O), 1693ν(C=O), 1641 ν(C=C). $^1H$ NMR (400 MHz, $CDCl_3$, δ, ppm): 2.312 (s, 3H, CO-$CH_3$), 2.466 (s, 3H, CO-$CH_3$), 7.603-7.731 (m, 4H, ArH), 8.258 (s, 1H, CH). Anal. Calcd. for $C_{11}H_9ClO_2$ C, 63.32; H, 4.35. Found: C, 63.51; H, 4.41 %.

### 2.4. Methyl 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(3-nitro phenyl)pyridine-3-carboxylate (IIIa)

Compound **IIa** (5.0 g, 0.021 mol) and compound **I** (2.3 g, 0.023 mol) were added to a three-necked flask containing 20 mL of dioxane, refluxed for 15 h under stirring. The solvent was removed under vacuum distillation. On slow cooling to room temperature, the products appeared as a yellow precipitate which was recrystallized in 15 mL acetone, and chromatographed on silica, elution was carried out initially with ethyl acetate:petroleum ether (1:1) mixture, the yellow crystal was obtained (6.27 g, 0.019 mol) with a yield of 93.2% and melting point, 193-195 °C. *Methyl 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylate* (**IIIa**): FT-IR (KBr, $cm^{-1}$): 3379 ν(N-H), 3010 ν(C-H), 1722 ν(C=C), 1695 ν(C=C), 1687 ν(C=O), 1594(C=O) (ester), 1474, 1450, 1277. $^1H$ NMR (400 MHz, $CDCl_3$, δ, ppm): 2.219 (s, 3H, CO-$CH_3$), 2.342 (s, 3H, $CH_3$), 2.401 (s, 3H, $CH_3$), 3.724 (s, 3H, $COOCH_3$), 5.180 (s, 1H, CH), 6.262 (s, 1H, NH), 7.414-8.095 (m, 4H, ArH). MS (m/z): 330[$M^+$]. Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 61.81; H, 5.49; N, 8.48. Found: C, 63.51; H, 5.61; N, 8.29 %.

### 2.5. Methyl 5-acetyl-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 dioxane as solvent, refluxed for 18 h under vigorous stirring, then vacuum distilled, 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-acetyl-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=C), 1664 ν(C=C), 1660 ν(C=O), 1580 ν(C=O)(ester), 1398, 1242, 1141. $^1H$ NMR (500 MHz, $CDCl_3$, δ, ppm): 2.271 (s, 3H, $CH_3$), 2.323 (s, 3H, $CH_3$), 2.371 (s, 3H, $COCH_3$), 3.672 (s, 3H, $COOCH_3$), 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 $C_{17}H_{18}ClNO_3$: 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 acetoacetate 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 1**. Different conditions of the synthesis of compound **I**.

| The source of nitrogen | Temp., °C | Time, h | Solvent | Yield, % |
|---|---|---|---|---|
| Ammonium bicarbonate | 60 | 2.5 | Ethanol | 52.2 |
| Ammonia | 0 | 2 | - | 83.2 |
| Ammonium acetate | 110 | 2 | Toluene | 68.5 |

### 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 catalyst, the reaction time was around 20 h [11], but through using $H_2SO_4$-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-acetyl-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=C group (on the dihydropyridine cycle) appeared; the formation of dihydropyridine cycle was confirmed from the broad band appearing in the $^1H$ NMR spectrum at 5.180 (s, 1H, CH), Characterizations of the **IIIb** from IR and $^1H$ NMR spectra were similar to **IIIa**.

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

| Catalyst | Temp., °C | Time, h | Yield, % |
|---|---|---|---|
| Conc. sulfuric acid | 78 | 3.5 | 77.4（a） |
| | | | 74.6（b） |
| Piperidine acetate | 78 | 3 | 81.2（a） |
| | | | 82.3（b） |
| Piperidine acetate | 25 | 22 | 86.1（a） |
| | | | 91.8（b） |
| Acetic anhydride-conc. sulfuric acid | 0~5 | 1.5 | 92.0（a） |
| | | | 92.2（b） |

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.

***Acknowledgement***

The authors express their thanks to the South-Central University for Nationalities for financial support during this investigation

## References

[1]. Satish, K.; Poonam, S.; Kamal, K. *Tetrahedron* **2008**, *64*, 536-538.
[2]. Javid, S. M.; Mojarrad, V. D.; Carlos, V.; Edward, E. K. *Bioorg. Med. Chem. Lett.* **2005**, *13*, 4085-4091.
[3]. Muchchinatala, M.; Vidavalur, S.; Yerra, K. R. *J Mol. Catal. A: Chem.* **2006**, *260*, 179-180.
[4]. Churchil, A. A.; Kannan, S. *Appl. Catal. A: General* **2008**, *338*, 121-125.
[5]. Shi, D. Q.; Mou, J.; Tu, S. J. *Chinese J. Org. Chem.* **2004**, *24*, 1042-1044.
[6]. Saikat, D. S.; Parasa, H.; Dllip, K. *Catal. Commun.* **2008**, *9*, 709-714.
[7]. Zhang, B. L.; He, W.; Shi, X.; Huan, M. L.; Huang, Q. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 805-806.
[8]. Deng, L.; Xu, M. X. *Chem. Res. Appl.* **2002**, *14*, 233-234.
[9]. Lin, C. Z.; Ko, S. K. *Tetrahedron Lett.* **2005**, *46*, 5771-5774.
[10]. Zhang, X. Y.; Li, Y. Z.; Fan, X. S.; Qu, G. R. *Chinese Chem. Lett.* **2006**, *17*, 150-152.
[11]. Amini, M. A.; Golabchifar. A.; Dehpour A. R. *Drug Res.* **2002**, *52*, 21-26.
[12]. Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron* **2004**, *60*, 2311-2326.
[13]. Liu, H. C.; Feng, Y. Q. *Chem. Ind. Eng.* **2006**, *23*, 88-91.