STUDY ON FACTORS INFLUENCING SYNTHESIS OF ETHYL 3-AMINOCROTONATE

NGHIÊN CỨU CÁC YẾU TỐ ẢNH HƯỞNG ĐẾN TỔNG HỢP ETHYL 3-AMINOCROTONAT

Vu Minh Tan*, Nguyen Ngoc Thanh, Le Thi Hong Nhung, Nguyen Quang Tung, Nguyen Xuan Canh, Hoang Thanh Duc

ABSTRACT

β-amino crotonate are compounds of interest since they find use as intermediates for the synthesis of Ca channel blockers such as Nisoladipine, Benidipine, Nicardipine and Felodipine. The method is characterized by allowing reaction between ethyl acetoacetate and ammonium acetate in methanol solution at a room temperature, for 20 hours and molar ratio ethyl acetoacetate with ammonium acetate is 1:3. The structure of the obtained product were determined by IR, ^{1}H-NMR and LC- MS spectroscopic data.

***Keywords**: Ethyl 3-aminocrotonate, β-aminocrotonate, ethyl acetoacetate, felodipine.*

TÓM TẮT

β-Amino crotonate là hợp chất được quan tâm nhiều kể từ khi nó được biết đến là chất trung gian trong tổng hợp các chất ức chế kênh calci như Nisoladipine, Benidipine, Nicardipine và Felodipine. Tổng hợp ethyl β-aminocrotonat dựa trên phản ứng của ethyl acetoacetate và ammonium acetate trong dung môi methanol, ở nhiệt độ phòng, trong 20 giờ và tỉ lệ mol ethyl acetoacetate với ammonium acetate là 1:3. Cấu trúc của chất tổng hợp được xác nhận bằng các phương pháp phổ IR, ^{1}H-NMR và LC- MS.

***Từ khóa**: Ethyl 3-aminocrotonat, β-aminocrotonat, ethyl acetoacetat, felodipine.*

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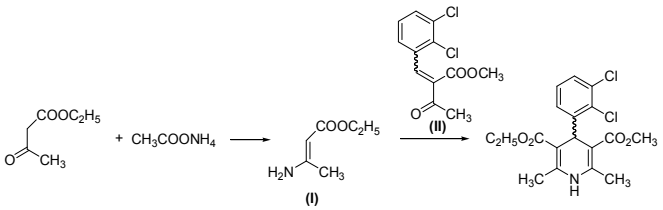
1. INTRODUCTION

Felodipine is a generic name of ethyl methyl 4-(2,3-dichlorophenyl)- l,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate, which is a calcium channel blocker acting for a long period of time and is well known for their effectiveness in the treatment of cardiovascular disease such as angina pectoris and hypertension [1-5]. Industrial synthesis of felodipine substances is multistep:



β-Enamino esters are useful intermediates in organic synthesis as synthons for the construction of biologically active compounds such as dopamine auto-receptor agonists [6], acetylcholinestersase inhibitors [7] and anticonvulsans [8]. On the other hand, substituted β-amino esters are useful intermediates for synthesis of heterocycles like pyrydinones, quinolones, oxazoles, pyrroles, isoxazoles [9-12],…

The synthesis of ethyl 3-aminocrotonate comprising reacting ethyl acetoacetate with a base as ammonia or ammonium acetate in presence of an organic solvent and an acid catalyst.

The solvent employed for a reaction of the starting materials can be any organic solvent that dissolves the ammonium salt sufficiently so as to promote the desired reactions. Such solvent need not be anhydrous. Thus, common, low-boiling solvents such as the aromatic solvents, e.g., benzene, toluene, etc.; aliphatic alcohol solvents, e.g., methanol, ethanol, etc.; and the Freon solvents can be used. The solvent of preference herein is ethanol, methanol, or mixtures thereof or solvent free [13-15]. Ratio of base and ethyl acetoacetate is 1:3 to 3:1 [14]. Catalyst is an aliphatic carboxylic acid selected from acetic acid and n-propanoic acid [14]. The reaction is performed at a temperature ranging between 20-60°C [14].

In order to optimize the reaction conditions of ethyl acetoacetate and ammonium acetate, in this study we examined the effect of reaction solvent, reaction time, molar ratio ethyl acetoacetate with ammoni acetate on the synthesis of the key intermediate of the felodipine synthesis and optimized the conditions of its preparation. Study on factors influencing synthesis of ethyl 3-aminocrotonate by thin layer chromatography.

2. EXPERIMENTAL

IR spectra were recorded by Impact 410-Nicolet on KBr pellets. ^{1}H-NMR spectra were recorded by Avance Spectrometer (Bruker, Germany) at 500 MHz, using DMSO-d_6 as solvent and TMS as an internal standard. LC-MS were recorded by LC-MS-ORBITRAP-XL and 5989B Hewlett – Packard Mass spectrometer.

Experiments were performed with ethyl acetoacetate (99%), ammoni acetate (99%), isopropyl alcohol (99%), ethanol (99%), methanol (99%), t-buthanol (99%),

acetonitrile (99%), n-hexane (99%), chlorofom (99%), ethyl acetate (99%). Thin layer chromatography (TLC) used pre-coated silica gel 60 F_{254} (Merck) and column chromatography (CC) was performed using a silica *gel* (Kieselgel 60, 70 -230 mesh, Merck).

Effect of solvent on the yield of ethyl 3-aminocrotonate (general procedure):

A solution of ammonium acetate (3.312 g, 0.036 mole) and 1.53 ml (0.012 mole) ethyl acetoacetate were dissolved in 1,45 ml methanol and stirred for 20 hours at the room temperature.

The extent of the reaction was monitored by thin-layer chromatography (solvent: 25% EtOAc/hexanes). Once the starting material was no longer detected, the solvent was evaporated. The residue was dissolved in 30 ml CH_2Cl_2 and extracted three times with brine. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated.

Ethyl 3-aminocrotonate was purified by column chromatography (adsorbent: silica *gel*; eluting solvents: 10-25% EtOAc/n-hexanes). The resulting product is a colorless liquid.

Study on other factors influencing synthesis of ethyl 3-aminocrotonate was conducted similarly.

3. RESULTS AND DISCUSSION

3.1. Structure of MBI

The structure of the obtained product (**I**) were determined by IR, ^{1}H-NMR, and LC-MS spectroscopic data.

The IR spectra of compound (**I**) show the characteristic absorption bands at 1716.31 cm^{-1} (C=O ester), 1660.16 cm^{-1} (C=O ketones), 3452.91 cm^{-1} and 3337.34 cm^{-1} (υ_{NH}). Besides, functional groups signs like aromatic C-H bond at 2981.9 cm^{-1}, C-O bond at 1162.2 cm^{-1} and other groups also appeared on IR spectra.

ESI (+)-MS/MS of intermediate $[M + H]^+$ of m/z 129.8 and $(M+Na)^+$ of 152.8. Anal. Calcd for $C_6H_{11}NO_2$.

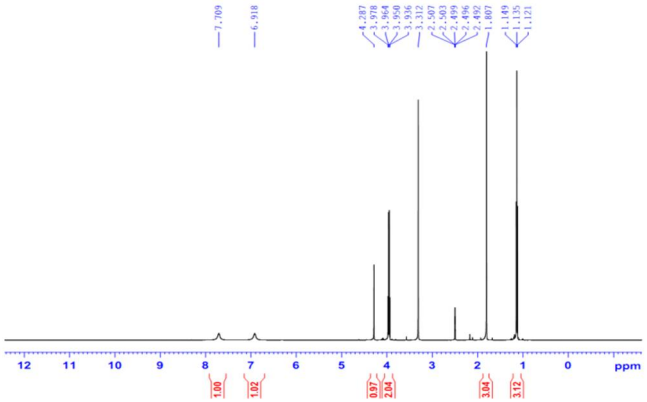
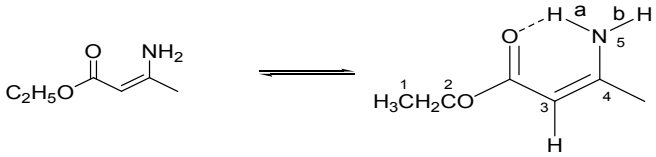


Figure 1. ^{1}H-NMR of compound (I)

^{1}H-NMR spectroscopies of the ethyl 3-aminocrotonate (**I**) (Figure 1). In ^{1}H-NMR spectra of (**I**), the placement of the hydrogens in the molecule showed that only the *Z*- forms were present.



^{1}H-NMR spectrum (DMSO-d6), δ, ppm: 1.149 -1.121 (3H, t, J = 7.0 and 7.0 Hz, $\underline{CH_3}CH_2$); 3.978 – 3.936 (2H, q, J = 7.0 and 7.0 Hz, $CH_3\underline{CH_2}$); 4.287 (1H, s, H-3); 1.807 (3H, s, 4-CH_3); 7.709 (1H, s, H-5a) and 6.918 (1H, s, H-5b).

3.2. Effect of solvent on the yield of (I)

Since solvent properties play a crucial role in organic synthesis, the effect of solvent was studied for synthesis of ethyl 3-aminocrotonate. The reaction was studied for 20 hours at the room temperature, and ammoninum acetate and ethyl acetoacetate mole ratios is 3:1. The comparative results for (**I**) obtained using different solvents are summarized in table 1 and it was found that methanol was a more economical and efficient solvent for the present transformation.

Table 1. Effect of solvent on the yield of ethyl 3-aminocrotonate

Entry	Solvent	Yield (%)
1	**Methanol**	**92.1**
2	Ethanol	84.4
3	Isopropyl alcol	73.7
4	*t*-Buthanol	74.3
5	Acetonitrile	68.6
6	Benzene	52.8
7	Totuene	50.9
8	solvent free	78.3

3.3. Effect of time on the yield of MBI

In order to obtain the best reaction time, the effect of reaction time on the % yield of major product was studied (Table 2). The reaction was progressed at room temperature and methanol as solvent.

Table 2. Effect of reflux time for the reaction of ethyl acetoacetate with ammonium acetate

Entry	Reaction time (hs)	Yield (%)
1	14	47.8
2	15	49.3
3	16	55.5
4	17	66.4
5	18	78.9
6	19	85.6
7	**20**	**92.0**
8	21	80.3
9	22	74.9

As shown in table 2, ethyl 3-aminocrotonate yield increased and then decreased with increasing reaction time because the appearance of by-products, resulting in decreasing yield. Therefore, 20 hours was chosen as reaction time under experimental conditions.

3.4. Effect of mole ratio on the yield of ethyl 3-aminocrotonate

Experiment was conducted by changing ammonium acetate use level in methanol, at room temperature and reaction time was 20 hs. The results are recorded in table 3.

Table 3. Effects of mole ratios on the yield of ethyl 3-aminocrotonate

Entry	Ammoninum acetate and ethyl acetoacetate mole ratios	Yield (%)
1	1.0:3.0	57.5
2	1.0:2.0	69.5
3	1.0:1.0	76.8
4	2.0:1.0	86.2
5	**3.0:1.0**	**91.8**
6	4.0:1.0	84.3
7	5.0:1.0	79.6

As shown in table 3, with gradual increase in ammonium acetate ethyl acetoacetate mole ratio, yield of ethyl 3-aminocrotonate increased and then decreased; when ammonium acetate ethyl acetoacetate mole ratio increased to 3.0:1.0 maximum yield was achieved.

Thus 3.0:1.0 was chosen as ammonium acetate ethyl acetoacetate mole ratio.

Ammonium acetate in this reaction is in equilibrium with ammonia and acetic acid. Even though the salt is favored in the equilibrium the ammonia and acetic acid can still react in the mechanism of the formation of ethyl 3-aminocrotonate (Figure 2).

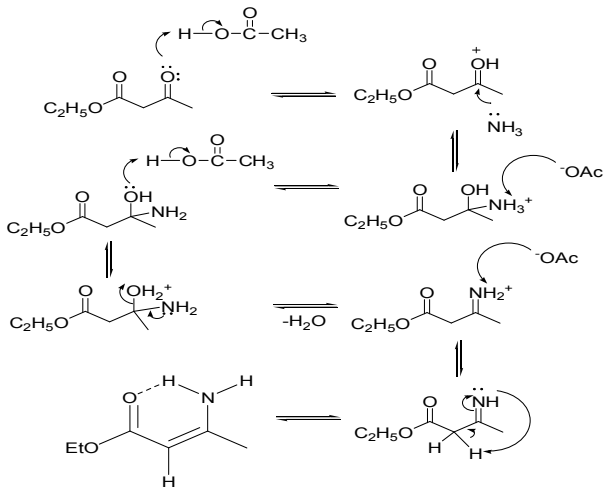


Figure 2. Proposed mechanism for the production of ethyl 3-aminocrotonate

4. CONCLUSION

We have found that the synthesis of ethyl 3-aminocrotonate from ethyl acetoacetate and ammonium aceatte is a viable. Optimum process conditions for synthesizing ethyl 3-aminocrotonate: methanol as solvent; reaction time was 20 hours; ammonium aceate: ethyl acetoacetate mole ratio was 3.0:1.0. This product was purified and has been isolated with 92% yield. The structure of ethyl 3-aminocrotonate were determined by IR, ^{1}H-NMR and LC-MS spectroscopic data.

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THÔNG TIN TÁC GIẢ

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