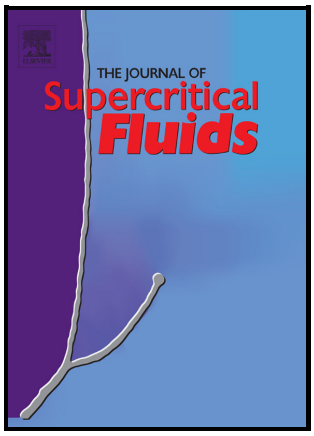
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An Efficient and Green Synthesis of 1,4-Dihydropyridine Derivatives Through Multi-Component Reaction in Subcritical EtOH

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Abstract

A simple, environmentally friendly and highly efficient method has been developed for the synthesis of 1,4-dihydropyridine compounds. A number of aromatic aldehydes, ethylaceto acetate and urea converted into corresponding in l,4-Dihydropyridine derivatives via one-pot multicomponent reaction in sub-critical ethanol. This study shown that 1,4-dihyropyridines can be synthesized in sub-critical ethanol and has the advantage of excellent yields, short reaction time, and simple work-up conditions.

Keywords: 1,4-dihydropyridines, Hantzsch reaction, subcritical ethanol, multicomponent reaction

1. Introduction

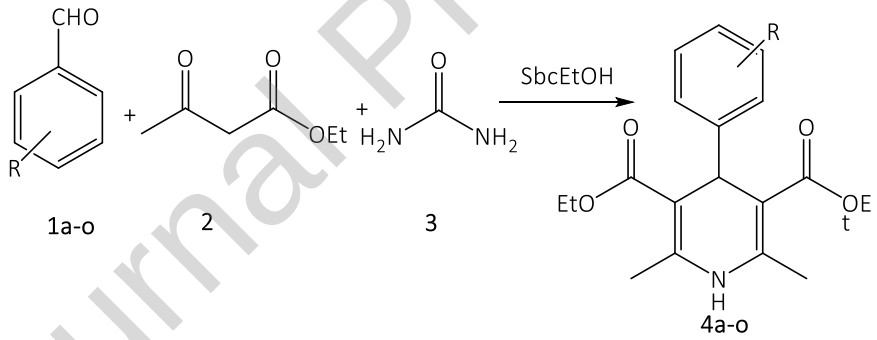
In synthetic organic chemistry, to reduce costs and help to conserve resources, development of new, green and efficient techniques continues to growing importance. Using supercritical fluids as reaction media and sometimes as catalyst, is an interesting basic approach along these lines. As well as supercritical carbon dioxide which is most widely used alternative solvent for organic synthesis, subcritical and supercritical water and supercritical diethyl ether are used as green solvents [1-3]. While low critical temperature and pressure of CO_2 (Tc: 31°C and Pc: 73 bar) makes it a widely used alternative solvent in organic synthesis and natural products extraction [4-6] subcritical or supercritical ethanol (EtOH) is not a common solvent for organic synthesis. However, due to relatively low critical temperature (241^{o}C) and the pressure (62.5 bar) subcritical or supercritical EtOH may be considered as a mild reaction media for organic synthesis on behalf of green chemistry.

1,4-Dihydropyridines are an important class of heterocyclic compounds in drug and pharmaceutical due to having various biological activities, such as bronchodilator, vasodilator, geroprotective, hepatoprotective, antitumor, antidiabetic, and anti-atherosclerotic. 1,4-dihydropyridines are also good intermediates for the synthesis of several alkoloids and a calcium channel antagonist, nifedipine, felodipine, etc. [7,8].

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The Hantzsch method is a one-pot multicomponent reaction (MCR) of an aldehyde with ethyl acetoacetate and ammonia either in acetic acid or in an alcohol was developed for classical synthesis of 1,4-DHPs. MCRs have great attention due to their simple procedures, superior atom economy and high selectivity [9,10]. However, long reaction times, low yields of the corresponding 1,4-DHPs and harsh reaction conditions are the main disadvantages of Hantzsch method. A number of modified methods which use solvent media such as ethanol, methanol and acetonitrile or several solvent-free procedures have been reported. Although these methods have potential application, they suffer from unsatisfactory yields, expensive and toxic reagents, and long reaction times [11-18].

Hence, considering the importance of the development of an efficient and environmentally benign method for the preparation of Hantzsch reaction products is still an attractive research area. As a continuation of our research on the applications of subcritical fluids in organic synthesis [1-3], we wish to report an eco-friendly, efficient, and high to excellent yield one-pot synthesis of Hantzsch 1,4-dihydropyridine derivatives in subcritical EtOH (SbCEtOH) (Scheme 1).



Scheme 1. One-pot synthesis of Hantzsch 1,4-dihydropyrimidines under SbCEtOH conditions

Although, an eco-friendly and very efficient method for the synthesis of 1,4- DHPs based on imidazole moiety in EtOH at ambient temperature and 60°C was reported by Sharma *et al.* [19]. The yield of imidazole based 1,4- DHPs was between 40 and 60%. We should mention that there are some differences between our new method and Sharma's. For example they used 2-butyl-5-chloro-1H-imidazole-4-carbaldehyde as an aromatic aldehyde compound which may behave as a base catalyst and decreases the activation energy of Knoevenagel reaction which is the key reaction during the synthesis and then increases the product yield. In our method, no any basic aromatic aldehyde compound which may increase the basicity of reaction media or any basic catalyst was used. On the other hand, SbCEtOH is less polar and has less hydrogen bond donation than ambient EtOH. When all these evaluated together, as an

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alternative reaction media, SbCEtOH provides very good and comparable yields for the synthesis of 1,4-Dihydropyridines in 60 min .

2. Materials and methods

2.1. Instrumentation Details

Melting points were determined using an Electrothermal 9100 instrument. Elemental analyses were measured on a Thermo Flash 2000 Organic Elemental Analyzer. GC-MS analysis were performed on a Finnigan-Trace GC–MS instrument. ^{1}H and ^{13}C NMR spectra were recorded in $DMSO_4$-d_6 [using the solvent peak as internal reference ($DMSO_4$-d_6 : δ H 2.50; δ C 39.51) on a Bruker Avance III 400 MHz spectrometer operating at 400 MHz and 100 MHz, respectively.

2.2. Typical Procedure for the Synthesis of dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylate

All chemicals were obtained from commercial sources and were used without further purification. All reactions were carried out in a high temperature high pressure 25 mL SS316 batch reactor. A mixture of arylaldehyde (5 mmol), ethyl acetoacetate (5 mmol), and urea (7,5 mmol) was mixed in the reactor with 12.5 mL ethyl alcohol. The reactor was fitted with ¼ in stainless steel Swagelok tube fittings, pressure gauche and thermocouple. The reaction conditions were 150°C and 60 min. Reaction time was started from the moment the reaction temperature was reached (almost 20 min), and it does not include the time required to cool the system (20 min). The pressure was depend on the reactor content. After completion of the reaction, the reactor was cooled to room temperature and pressure in a cooling pot. Later, the reactor washed with Et_2O. At the end of the reaction, the cooled mixture is poured onto the water-ice mixture (30 ml), the precipitated solid is filtered off, washed with cold water and recrystallized with ethanol to afford the pure product. After recrystallization of the product, the yield was calculated by considering of the ratio of pure products to initial amount of aromatic aldehydes. The structural data for 4a [20], 4b [22], 4c [26], 4d [20], 4f [21], 4g [27], 4h [25], 4i [21], 4j [20], 4k [20], 4l [20], 4m [24], 4n [23], 4p [20] and 4q [28] is in accordance with the results reported in the literature.

2.3. GC–MS analysis

GC–MS analysis was carried out by using a Finnigan-Trace GC–MS instrument. One microliter of sample volume was injected using split method with 50 split ratio and, chromato-graphic separations were performed with a Zebron ZB-5capillary column (5% phenyl–95% dimethylpolysiloxane, 0.25 mm i.d. × 60 m, film thickness 0.25 μm). Helium

was used as the carrier gas with flow rate 1.0 mL/min. The column temperature reached to 240 ^{o}C from 50 with 3 ^{o}C/min. The sample size was 2 mL and the injection port temperature was 250 ^{o}C. The ionization voltage applied was 70 eV, mass range m/z 41–400 a.m.u.

2.4. ^{1}H NMR and ^{13}C NMR analysis

^{1}H and ^{13}C NMR spectra were recorded in $DMSO_4$-d_6 [using the solvent peak as internal reference ($DMSO_4$-d_6 : δ H 2.50; δ C 39.51) on a Bruker Avance III 400 MHz spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiples), br s (broad singlet).

3. Results and Discussion

In classical Hantzsch reaction, 1,4- dihydropyridines were synthesed via multi-component one pot condensation reaction of aldehyde, alkyl acetoacetate and aqueous ammonium hydroxide in ethanol. Later, ammonium acetate, ammonium carbonate, formamide were also used as a nitrogen source [7,29].

In this study, initially, we planned to repeat a simple Hantzsch reaction in SbCEtOH instead of refluxe in EtOH as Hantzsch done. Hence, one pot Hantzsch reaction was performed between benzaldehyde **1a** (5 mmol) ethyl acetoacetate **2** (5 mmol) and aqueous ammonium hydroxide **(5** mmol) were reacted in SbCEtOH at 220°C for 60 min without using any catalyst. However, at the end of this reaction we observed some condensation products of benzaldehyde and acetone instead of Hantzsch product. It was understandable, because ethyl acetoacetate was decarboxylated into acetone under this condition. Because very little amount of water of aqueous ammonium hydroxide was sufficient for the decarboxylation of ethyl acetoacetate. Then, we decided to use urea as the nitrogen source , and attempted to carry out one pot Hantzsch reaction between benzaldehyde **1a** (5 mmol) ethyl acetoacetate **2** (5 mmol) and urea **3** (7.5 mmol) in SbCEtOH at 220°C for 60 min. As before, we did not use any catalyst in this experiment. When the reaction was completed, reactor content was analyzed with GC-MS. GC–MS analysis showed that dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) was completed successfully. After this promising result, it is needed to study the effect of various temperatures, the amount of EtOH and other subcritical alcohols (methanol, propanol and isopropanol) on the yield. All results are presented in the following section.

3.1. Effect of reaction temperature and the amount of EtOH

At first, to determine optimal conditions for the green synthesis of the dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates in SbCEtOH, two reaction temperatures (150 and 220 ℃) and various solvent amounts (10.0, 12.5 and 15.0 mL) were tested. Totally 17 DHPs were syntheses

with very good yields (Scheme 1). A model reaction of benzaldehyde **1a** (5mmol) ethyl acetoacetate **2** (5 mmol) and urea **3** (7.5 mmol) was used for optimization studies. The product of the model reaction was dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**). Initially, the optimal reaction temperature was investigated, and test reactions were carried out at two different temperatures (150 and 220°C) with 60 min reaction time and 10 mL EtOH. The yield of **4a** was calculated as 51.7% for 150 °C and 54.7% for 220 °C. Since we didn't see any dramatical differences between these results, we decided to investigate the any effect of solvent amount on the yield of compound **4a** at 150 °C and 220°C**.** As seen from Table 1, at 150 °C, with the increase of solvent amount from 10 mL to 12.5 mL, the yield of **4a** increased from 51.7% to 56.0%.

Table 1. Optimization study results: Effect of amount of EtOH

Temperature °C	EtOH mL	Yield %
150		
	10.0	51.7
	12.5	56.0
	15.0	48.1
220		
	10.0	54.7
	12.5	50.1
	15.0	47.2

However, a further increase in the amount of EtOH (15 mL) decreased the yield of **4a** to 48.1%. Similar tendency was observed in case of reactions at 220 °C. Since the best yield of **4a** (56.0%) was received with 12.5 ml of EtOH at 150 °C and 60 min reaction time, we decided to continue to syntheses of dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylate derivatives under same conditions. During the all reactions, pressure was almost similar and 9.1 atm. The results of optimization studies were collected in Table 1.

After optimization studies, to be sure the effect of the reaction temperature on the yield of target product, we performed the synthesis of model compound dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) at 125, 180 and 200°C with 12.5 mL EtOH. The results are collected in Table 2.

Table 2. Optimization study results: Effect of temperature in EtOH

Entry	Temperature °C	Pressure atm	Yield %
1	125	<2	Trace
2	150	9,1	56.0
3	180	9,1	45.0
4	200	9,8	32.0

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5	220	9.8	50.1

It was observed that, in our batch reactor system, the pressure of reactor content wasn't enough to maintain EtOH in subcritical region when the temperature lower than 150°C (Table 2, Entry 1). At 180 and 200°C, the yield of **4a** was lower than those of 150°C (Table 2, Entries 3 and 4). As a last attempt, synthesis of model compound **4a** was performed at supercritical EtOH conditions (250°C). According to the GC-MS results, relative yield of 4a was only 25.6%. Unlike other experiments, some condensation reaction products of benzaldehyde **1a,** ethyl acetoacetate **2** and acetone (decarboxylation product of **2**) were observed as side products and the relative amount of them was 66.1%. Hence, all these results confirmed that 150°C is better for the synthesis of dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates in SbCEtOH.

3.2. Comparation Effect of SbCEtOH with subciritcal methanol, subcritical propanol and subcritical isopropanol on the yield of model reaction

We also compared the efficiency of SbCEtOH on the yield of the yield of model compound **4a** with subciritcal methanol, subcritical propanol and subcritical isopropanol. The amount of all the solvents used were 12.5 ml. As seen Table 3, except SbCEtOH, other alcohols were very poor for the production of dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates **(4a)**.

Table 3. Effect of the subcritical alcohols on the yield of compound **4a**

Entry	Alcohol	Temperature (^{o}C)	Pressure atm	Yield (%)
1	Ethanol	150	9.1	56.0
2	Methanol	150	7.8	40.0
3	2-propanol	150	7.8	34.8
4	Propanol	150	7.8	29.3
5	Ethanol	220	9.8	50.1
6	Methanol	220	18.0	38.8
7	2-propanol	220	11.2	28.0
8	Propanol	220	11.2	26.1

After all these results we decided to continue the synthesis of 1,4-DHP derivatives at 150°C by using 12.5 mL EtOH.

The positive effect of SbCEtOH may be explain with its physiochemical properties. At 150°C, SbCEtOH has higher Kamlet-Taft dipolarity/polarizability and Kamlet-Taft hydrogen bond donation than those of at 220°C (Table 4). In addition, higher density of SbCEtOH at 150°C makes it a better reaction media for one-pot synthesis of Hantzsch 1,4-dihydropyridine derivatives.

Some thermophysical properties of subcritical ethanol and subcritical methanol are shown in Table 4.

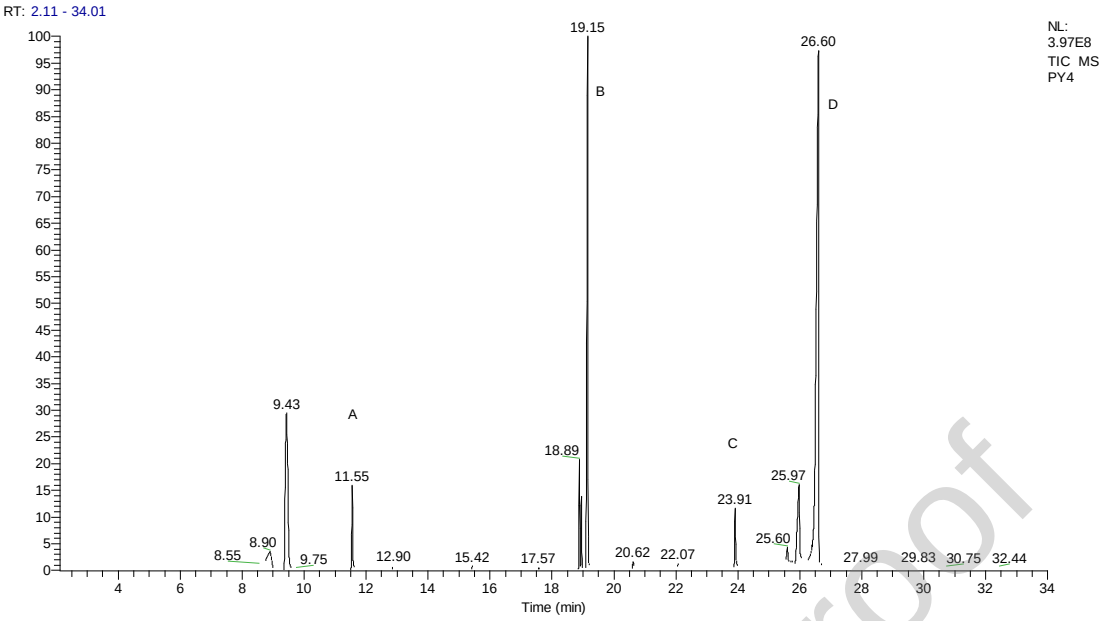
Table 4. Properties of sub-critical ethanol and methanol

	EtOH		MeOH	
T/K	423	498	423	498
Density *r*/kg m-3	664.4 [32]	574.6 [32]	646.9 [33]	514.3 [33]
Viscosity, *h*/mPa s	-	-	0.141 [34]	0.034 [34]
Kamlet-Taft dipolarity/polarizability, *p** [13]	0.27	0.03	-	-
Kamlet-Taft H-bond donation α [31]	0,57	0.53	-	-
Kamlet-Taft H-bond acceptance β [31]	0.56	0.47	-	-
Dielectric constant , ε [35]	9.88	5.37	14.40	7.29

However, no such data were found for subcritical 1- propanol and subcritical 2-propanol. At ambient conditions, ethanol have highly hydrogen-bonded structure. However, with increasing temperature, Kamlet-Taft hydrogen bond donation ability (α), Kamlet-Taft dipolarity/polarizability (π*) and Kamlet-Taft hydrogen bond acceptance ability (β) and polarity decrease and at critical point, they reach to the lowest amount (Table 4) [30]. This phenomenon, makes ethanol less polar and able to dissolution of non-polar substance. On the other hand, liquid-like densities of SbCEtOH keeps its solvent power for to solvate polar solutes due to enough dipolarity and hydrogen bond donation/acceptance ability. At 150°C, Kamlet-Taft dipolarity/polarizability of SbCEtOH is 0.27 and Kamlet-Taft hydrogen bond donation is 0.57 while at 220°C they are 0.03 and 0.53, respectively [31] and densities are 664.4 kg m^{-3} at 150°C and 574.6 kg m^{-3} at 220°C [32]. Only densities of subcritical methanol are 646.9 kg m^{-3} and 514.3 kg m^{-3} at 150°C and 220°C, respectively [32]. At these two temperatures, density of 2-propanol is between 268.0 kg m^{-3} and 343.1 kg m^{-3}.

Before separation and purification of compound **4a,** we examined the reaction mixture by GC-MS. In GC chromatogram of **4a**, peaks of ethyl-3-aminocrotaoate which is product of the reaction of urea and ethanol, Knoevenagel condensation product, dimethyl-4-phenylpyridine-3,5-dicarboxylate (aromatization product of **4a**) and **4a** were observed (Figure 1).

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A: Ethyl-3-Aminocrotanoate

B: Knoevenagel condensation product

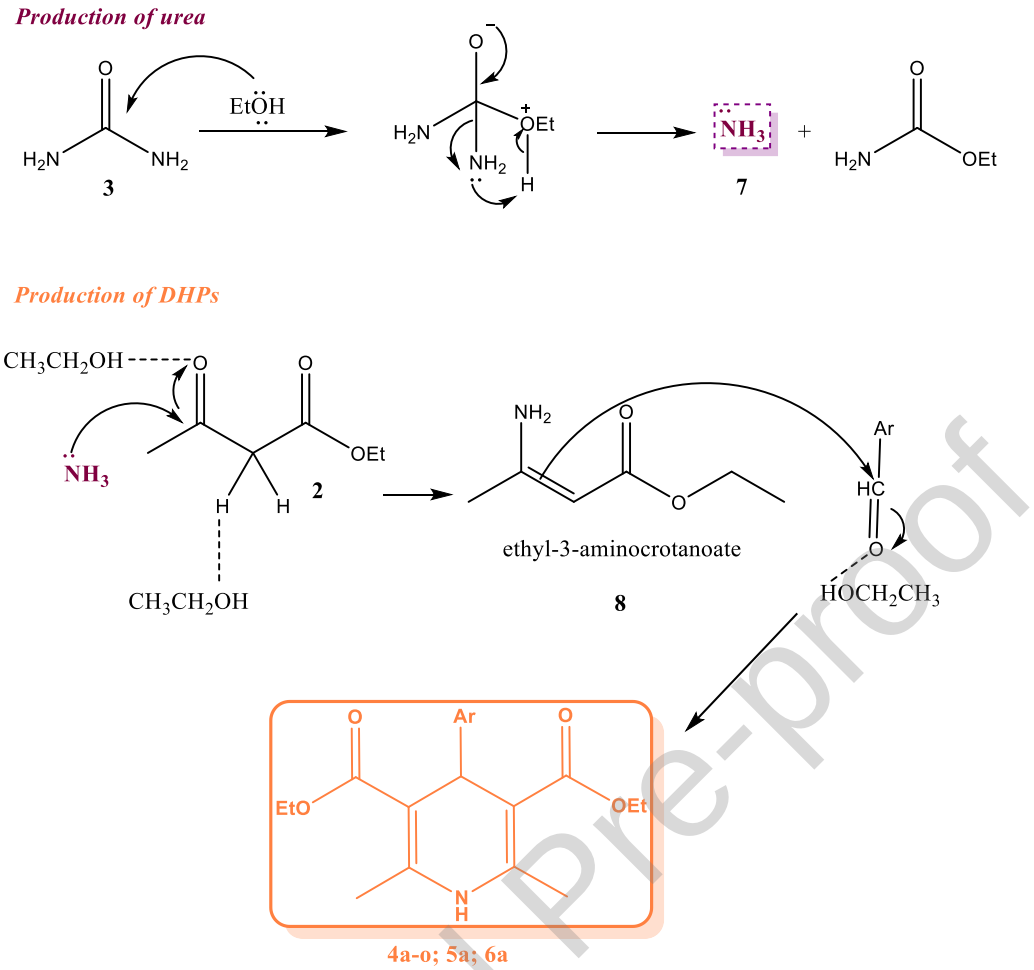
C: Dimethyl-4-phenylpiridine-3,5-dicarboxylate (aromatization product)

D: Dimethyl-4-pheny-1,4-dihydropiridine-3,5-dicarboxylate

Figure 1. GC chromatogram of the reaction mixture of dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **4a**

According to the these results a possible mechanism of the synthesis of 1,4-dihydropyridine in supercritical ethanol is given in Scheme 2.

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Scheme 2 Proposed mechanism for Hantzsch reaction under SbCEtOH conditions

Ammonium (**7**) was produced from reaction of urea (**3**) with ethanol and reacted with ethyl acetoacetate (**2**) to produce ethyl-3-amino crotanoate (**8**) (**A** in Figure 1). GC-MS analysis also shown Knoevenagel condensation product as key intermediate (**B** in Figure 1).

In mass spectral analysis, we obtained peaks at the particular mass of the compounds and base peak at *m/z*=252 (M^+- Ar, diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate ion) and, *m/z* 224 (CO lost from base peak*)* and, *m/z* 196 (2 CO lost from base peak*)* values are the major peaks in all compounds.

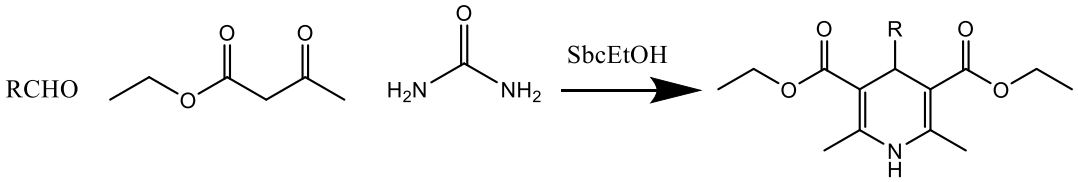
3.2. Synthesis of dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates in subcritical ethanol

To see the applicability of the method, a variety of aromatic aldehydes have been reacted with ethyl acetoacetate (**2**) and urea (**3**) in SbCEtOH at 150 °C and 60 min. We clearly observed that electronic and steric effects are important on the yield of DHP derivatives. The reaction of benzaldehydes which are bearing electron withdrawing groups (such as -NO_2, F, Cl and Br) gave excellent corresponding DHP yields (Entries 4-7, 11,12 in Table 5) while reactions of benzaldehydes

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donated with electron releasing groups (such as -OH and -OCH_3) resulted with very poor yields (Entries 2, 3,15 and 16 in Table 5).

Table 5. Synthesis of 1,4-DHPs in subcritical EtOH



Entry	R	Yield %
1	Ph	56.0
2	4-OH Ph	18.3
3	4-F Ph	91.1
4	3-NO_2 Ph	92.2
5	4-CF_3 Ph	92.2
6	4-Br Ph	94.7
7	2-Br Ph	26.4
8	2-Cl Ph	19.5
9	3-Cl Ph	68.1
10	4-Cl Ph	92.2
11	4-NO_2 Ph	96.6
12	4-OCH_3 Ph	79.3
13	4-CH_3 Ph	75.2
14	3,4,5-tri-OCH_3 Ph	35.6
15	4-OH-3,5-di-OCH_3 Ph	29.3
16	C_4H_3O	97.5
17	$C_{10}H_7$	34.2
18	C_5H_4N	-

On the other hand, regardless of whether electron releasing or electron withdrawing substituents on C-2 of benzaldehyde, probably due to steric effect, the yields of DHPs were very low (Entries 2, 8, and 9 in Table 5). In addition, in case of salicylaldehyde, we didn't synthesize corresponding DHP derivative. It may be explained H-bond interaction between -OH group on C-2 of salicylaldehyde and EtOH as well as steric effect. The formation mechanism of 1,4- DHPs is suggested to be as follows (Scheme 2). It was considered that the reaction starts with the formation of Ammonia (**7**)

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from urea (**3**) and EtOH. In the next step ammonia attacks to ethyl acetoacetate (**2**) which became a good electrophile due to hydrogen bonding with EtOH to afford compound **8**. It was also considered that hydrogen bonding of EtOH with α-hydrogen and carbonyl group of **7** further help to production of compound **8**. Finally, reactions between **8** and benzaldehydes (**1a-o**) produced corresponding 1,4-DHPs. Under this novel and green conditions, we also examined the reactions with 2-furancarboxaldehyde (**5**), 1- naphthaldehyde (**6**) and 2-pyridinecarboxaldehyde (**9**). Among these heteroaromatic and condensed aromatic aldehydes, 2-furancarboxaldehyde (**5**) was most reactive one and produced corresponding 1,4-DHP compound with an excellent yield (98%) while 2-pyridinecarboxaldehyde (**9**) was unreactive (Entries 16 and in Table 5, respectively). 1,4-DHP compound of 1- naphthaldehyde (**6**) obtained in moderate yield (34%, Entry 17 in Table 5).

We also observed a surprising result during Hantzch reaction in SbCEtOH. A compound (diethyl-2,6-dimethyl-4-phenyl-3,5-pyridinecarboxylate, **C** in Figure 2) was identified as aromatization product of **4a** during the synthesis.

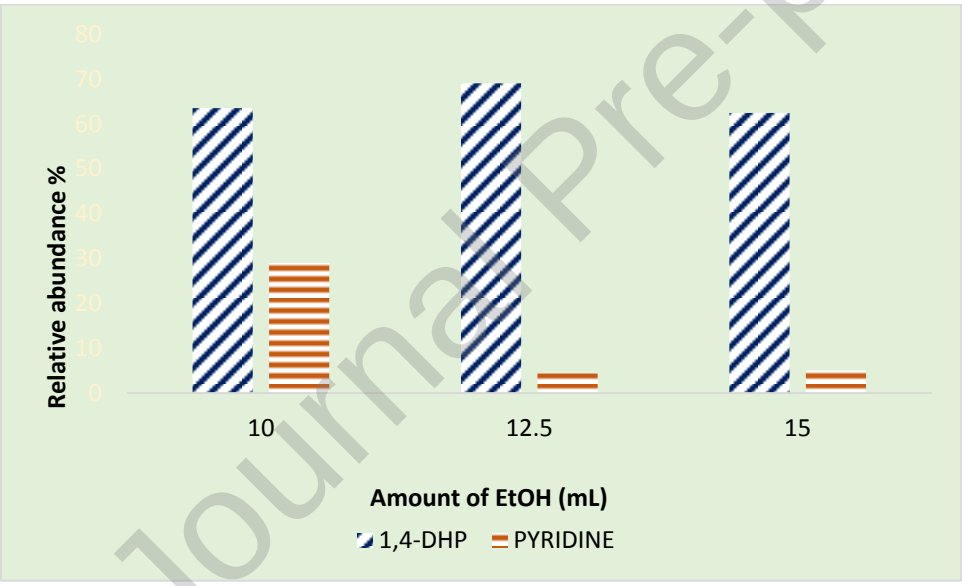


Figure 2. Effect of EtOH amount on the yield of **4a** and side product

Aromatization product, dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates were detected almost in all reaction mixtures. This result led us to think that there is a competition reaction between formation of 1,4-DHPs and their corresponding aromatization product, dihydropyridines (DHPs). We also realized that amount of EtOH has an effect on this competition. As seen from Figure 2, increasing the amount of EtOH decreased the yield of aromatization product while increasing the yield of 1,4-DHPs. The lowest aromatization product yield was observed when 12.5 mL EtOH which was chosen as optimum amount for this study, was used. Generally, aromatization of DHPs was performed by using strong

oxidants such as as MnO_2/bentonite [36-38], ceric ammonium nitrate (CAN) [39], phenyliodine (III) bis(trifluoroacetate) [40]. However, a mild reaction for the aromatization of DHPs with $AlCl_3$. $6H_2O$ as a mild and effective catalyst at 60 °C was also reported by Sharma et al [41], severe reaction conditions such as needing excess oxidants, long reaction times and moderate products yields were the main drawbacks of these methods. Even though, in this study, our main subject was to synthesis of 1,4-DHP derivatives in supercritical EtOH, this surprising result deserves further considerations since aromatization of 1,4-DHPs in supercritical EtOH without using any oxidants except air, didn't reported before.

4. Conclusion

In conclusion, 1,4-DHPs (**4a-q**) were synthesized from urea, ethyl acetate and aryl aldehydes in sub-critical EtOH, without using any other reagents. The suggested mechanism includes production of ammonia from EtOH and urea and Knoevenagel reaction of ethyl-3-aminocrotanoate with benzaldehydes. Although only two heteroaromatic aldehydes were tested, results are promising and these novel and green method could be extended for other heteroaromatic aldehydes. GC-MS analysis confirmed that aromatization products of 1,4-DHPs were also observed as side product.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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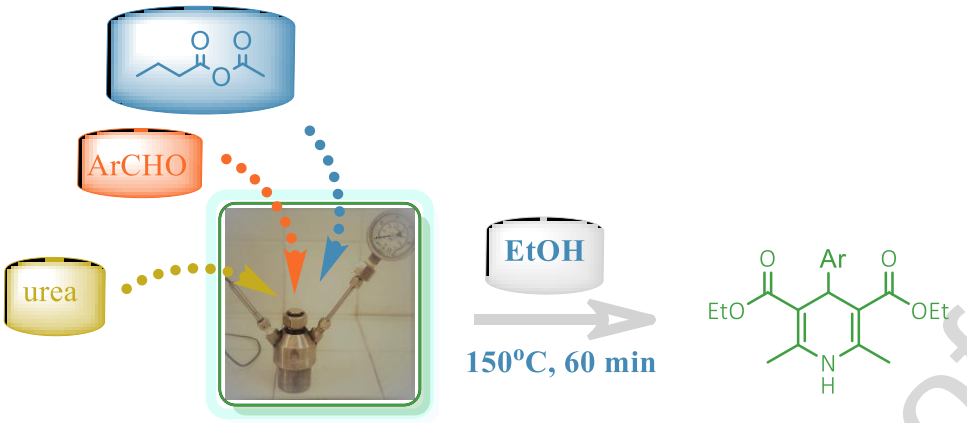
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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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HIGHLIGHTS

- First study on synthesis of 1,4-dihydropride derivatives in subcritical ethanol medium
- high efficiency, simple and environmentally friendly single-pot multi-component reaction
- 17 different 1,4-dihydropride derivatives obtained in high yields by simple and effective purification method

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