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College of Science
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Green and One-Pot, Synthesis of Hantzsch 1,4-Dihydropyridines Using Ball-Milling Solvent- Free Catalyst-Free Conditions.

A graduation research project
Submitted to the Department of Chemistry in partial fulfillment of the requirements for the completion of the degree of Bachelor of Science in Chemistry

By

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Under supervision

of

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Table of Contents

List of Tables

List of Figures

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ملخص

يعالج هدا المشروع البحثي استخدام طريقة تحضير فعالة وصديقة للبيئة لبعض مشتقات البايريمين من خلال استخدام تقنية الطحن بواسطة الكرات. هده التقنية لها اهمية كبيرة لكونها اقتصادية، بسيطة، صديق للبيئة و كدالك تمكن من الصول علي مردود مرتفع للمركبات المنتجة.

ABSTRACT

A novel process for one-pot synthesis of Hantzsch 1,4-dihydropyridine derivatives was developed through ball milling under solvent-free and catalyst-free conditions. The proposed method is economical, simple, and eco-friendly and provides high yields.

INTRODUCTION

1,4-Dihydropyridines are an important class of heterocyclic compounds in drug and pharmaceutical fields [1–3]. Hantzsch 1,4-dihydropyridines exhibit various biological activities, such as antitumor, vasodilator, bronchodilator, hepatoprotective, antidiabetic, geroprotective, and anti-atherosclerotic [4,5]. Compounds containing 1,4-dihydropyridines can be applied to several drugs, such as nifedipine, which functions as calcium channel antagonists [6] and intermediates in the preparation of alkaloids of natural products [7].

Several methods have been reported for the synthesis of Hantzsch 1,4-dihydropyridines under classical or modified conditions [8,9]. Nevertheless, the application of these methods with organic solvents and different catalysts leads to low yields of Hantzsch 1,4-dihydropyridines with long reaction durations. Scholars have also increasingly focused on reduction of any source of pollution. Thus, efficient, clean, and flexible synthesis methods must be developed.

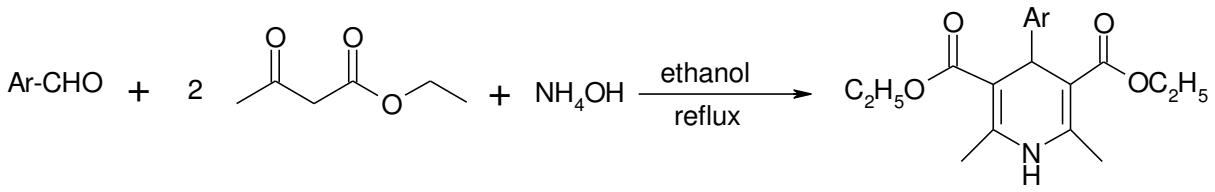
Solvent-less ball milling technique has been applied in organic synthesis because of its low cost, simplicity, and environment friendliness, as well as its ability to produce high yields.

The use of the ball milling technique in organic synthesis has gained increasing attention over the last decades [10,11]. Ball milling is used to synthesize various types of organic compounds for the preparation of phosphorus ylides [12], reductive benzylation of malononitrile [13], functionalization of Knoevenagel condensations [14], functionalization of fullerenes [15], coordination polymers [16], synthesis of nitrones [17], protection of diols/diamines [18], Suzoku-type reaction [19], synthesis of functionalized indan-1,3-diones [20], aldol reaction [21,22], Heck-type reactions [23,24], symmetrical and unsymmetrical thioureas [25], pyrano pyrimidine-dione synthesis [26], functionalized 2- amino-3-cyano-4H-pyrans [27], and synthesis of thioxo- and oxo-pyrimidine-5-carbonitriles [28].

This research applied ball milling to synthesize Hantzsch 1,4-dihydropyridines under solvent- and catalyst-free conditions.

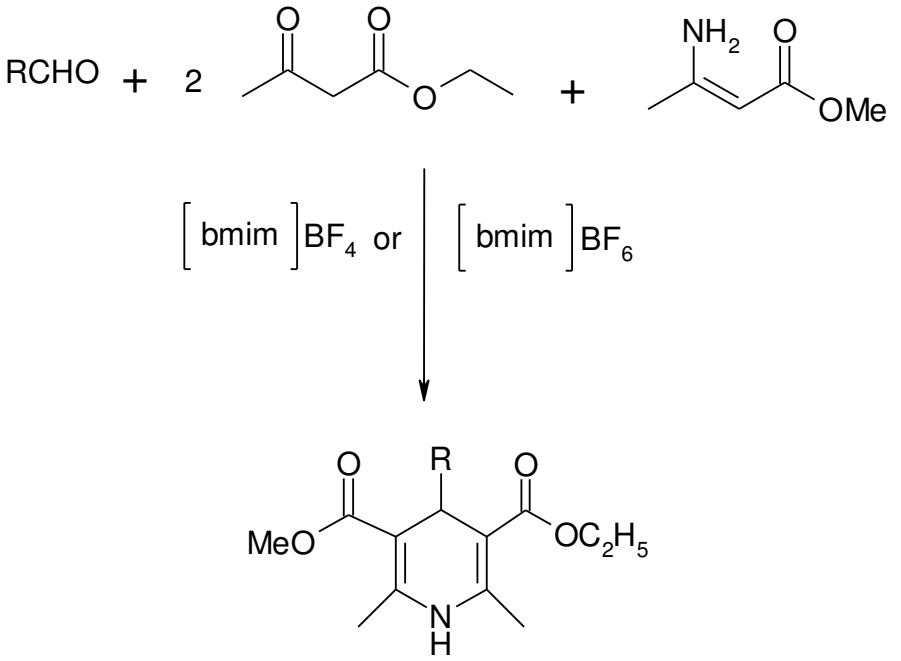
REVIEW OF LITERATURE

Hantzsch is the first to report the synthesis of 1,4-dihydropyridines via the condensation of aldehyde, ethyl acetoacetate, and ammonia salts in an alcohol reflux (Scheme 1) [29]. The reaction provided the desired products for a prolonged period of time and with low yields.



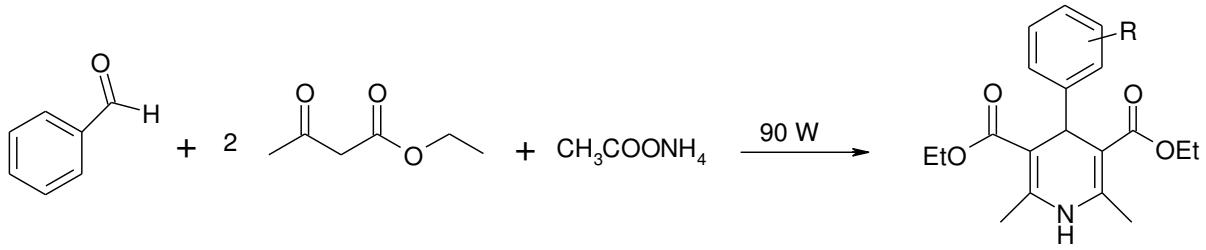
Scheme. 1 Synthesis of Hantzsch 1,4-dihydropyridines in ethanol reflux

Yadav et al. [30] developed a method to synthesize various 1,4-dihydropyridines and obtained satisfactory yields. The synthesis procedure involves the condensation of aldehyde, β-ketoester, and methyl 3-aminocrotonate in ionic liquids, such as 1-n-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-n-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) (Scheme 2).



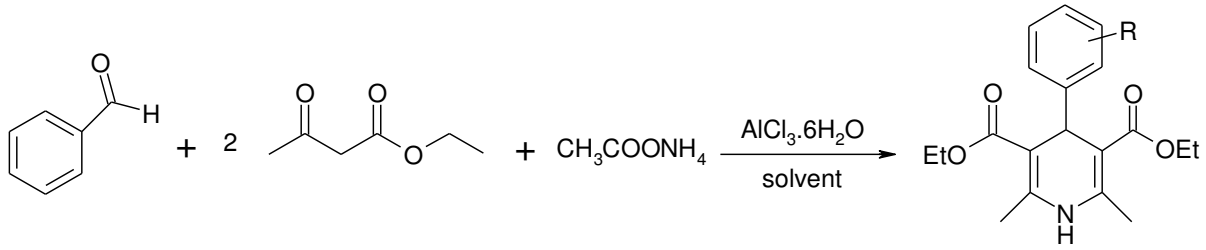
Scheme. 2 Synthesis of Hantzsch 1,4-dihydropyridines in [bmim]BF_4 and [bmim]PF_6

A simple, eco-friendly, cost-effective, and green method was developed for the synthesis of various 1,4-dihydropyridines with excellent yields (85%–95%) (Scheme 3) [31]. This method involves placing a mixture of benzaldehyde, ethyl acetoacetate, and ammonium acetate in a domestic microwave oven at 90 W for 3–5 min.



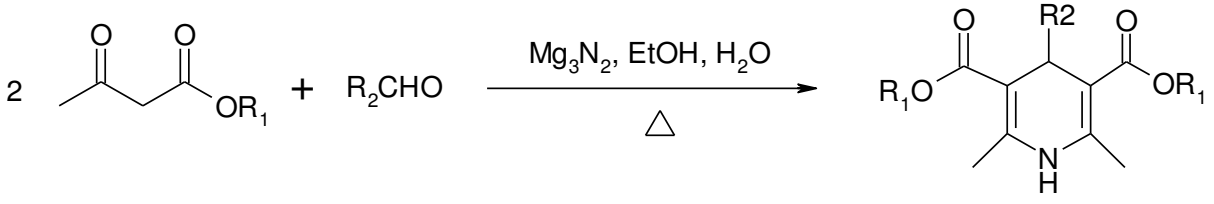
Scheme. 3 Facile one-pot condensation of 1,4-dihydropyridines

A simple one-pot four-component, green, and solvent-free condition was reported for the synthesis of 1,4-dihydropyridines (Scheme 4) [32]. The reaction produced the desired 1,4-dihydropyridines with high yields, and $AlCl_3$•$6H_2O$ was used as a mild and effective catalyst at 60 °C.



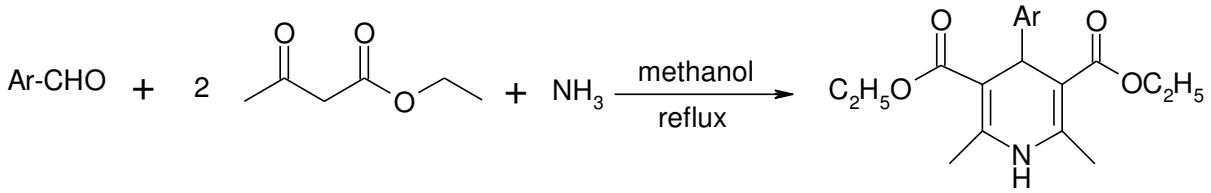
Scheme. **4** Synthesis of 1,4-dihydropyrimidines catalyzed by $AlCl_3.6H_2O$

Bridgwood et al. [33] synthesized 1,4-dihydropyridines via the condensation reaction of aldehyde, β-ketoester, and magnesium nitride (Mg_3N_2) as an ammonia source (Scheme 5).



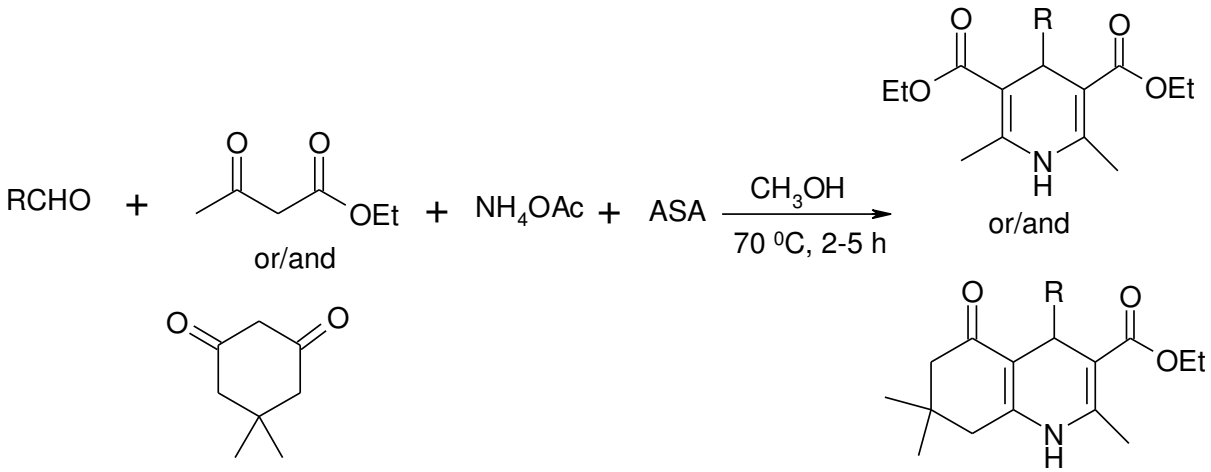
Scheme. **5** Synthesis of pyridine derivatives using (Mg_3N_2) as a source of ammonia

Harish et al. [34] also synthesized Hantzsch 1,4- dihydropyridines with good yields via the one-pot three component reaction of aldehydes, alkylacetoacetate, and ammonia in a methanol reflux (Scheme 6).



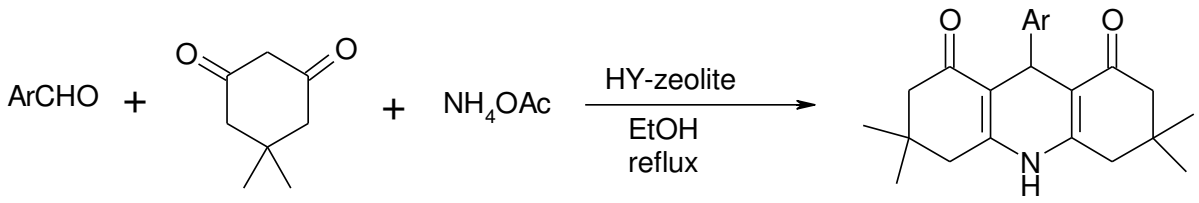
Scheme. **6** Synthesis of pyridine derivatives in methanol reflux

Arslan et al. [35] synthesized different 1, 4-dihydropyridines via the condensation reactions of aromatic aldehyde derivatives, ethyl acetoacetate/dimidone, and ammonium acetate in the presence of alumina sulfuric acid as a catalyst in methanol at the reflux temperature (Scheme 7).



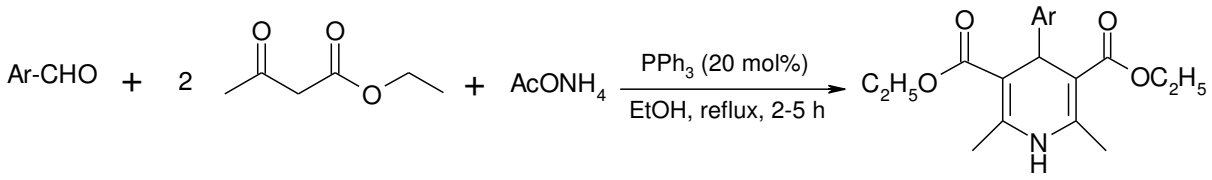
Scheme. **7** Synthesis of different 1,4-dihydropyridines in the presence of ASA

Mamaghani et al. [36] also developed a method to synthesize 1,4-dihydropyridine derivatives at reaction times of 2.5 h to 3.5 h by reacting aromatic aldehyde derivatives, dimedone, and ammonium acetate in an ethanol reflux with HY-zeolite as an heterogeneous catalyst (Scheme 8).



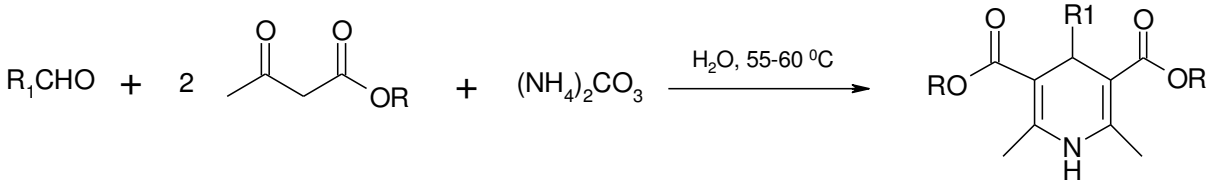
Scheme. **8** Synthesis of 1,4-dihydropyridines in the presence of HY-zeolite

Debache et al. [37] developed an effective one-step synthesis of Hantzsch 1,4-dihydropyridines (Scheme 9). The different reactions were performed in an ethanol reflux at reaction times of 2 h to 5 h. The products were obtained with high yields by using triphenylphosphine as a catalyst via the three-component reaction of aromatic aldehydes, ethyl acetoacetate, and ammonium acetate.



Scheme. 9 One-pot synthesis of 1,4-dihydropyridines using PPh_3 as catalyst

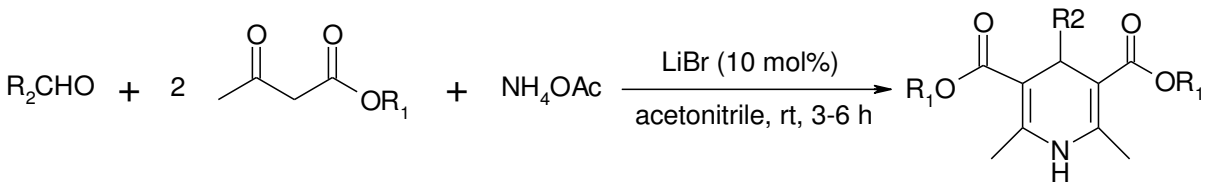
Tamaddon et al. [38] efficiently synthesized Hantzsch 1,4-dihydropyridines by using ammonium carbonate in water at 55 °C to 60 °C (Scheme 10). This method produced the Hantzsch products with higher yields than other methods. The authors mentioned that a competition was observed between the Biginelli and Hantzsch reactions with pyridine carbaldehydes.



Scheme. 10 Synthesis of Hantzsch 1,4-dihydropyridines using ammonium carbonate

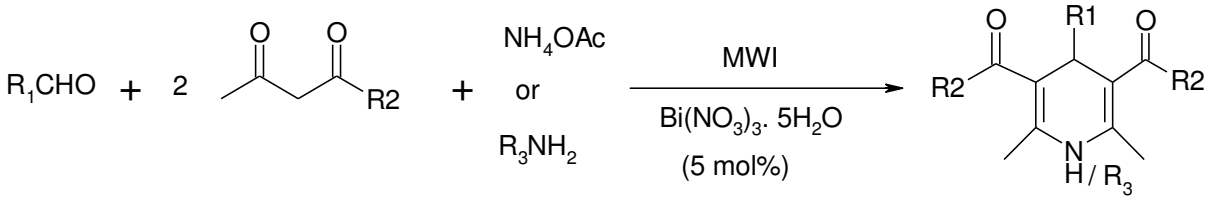
Yadav et al. [39] described the synthesis of Hantzsch 1,4-dihydropyridines with good yields by using a lithium bromide catalyst for the three-component condensation reaction of

aldehyde derivatives, β-ketoester, and ammonium acetate in acetonitrile at room temperature (Scheme 11).



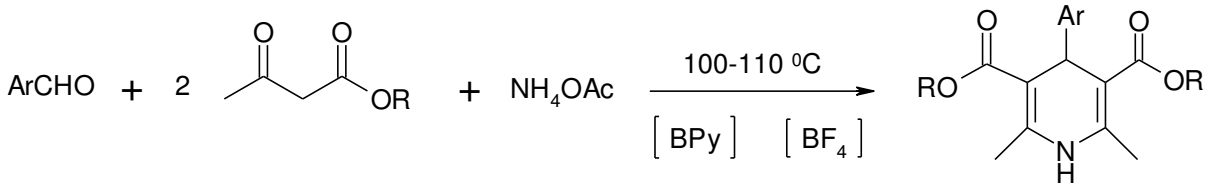
Scheme. 11 Synthesis of Hantzsch 1,4-dihydropyridines catalyzed by LiBr

The use of microwave irradiation for the synthesis 1,4-dihydropyridines has been described by Bandyopadhyay et al. [40]. The authors showed that the use of bismuth nitrate pentahydrate as a catalyst for the one-pot three-component reaction of aldehydes, 1,3-dicarbonyl compounds, and different amines/ammonium acetates under microwave irradiation provided the desired 1,4-dihydropyridines in a short time but with very high yields (Scheme 12).



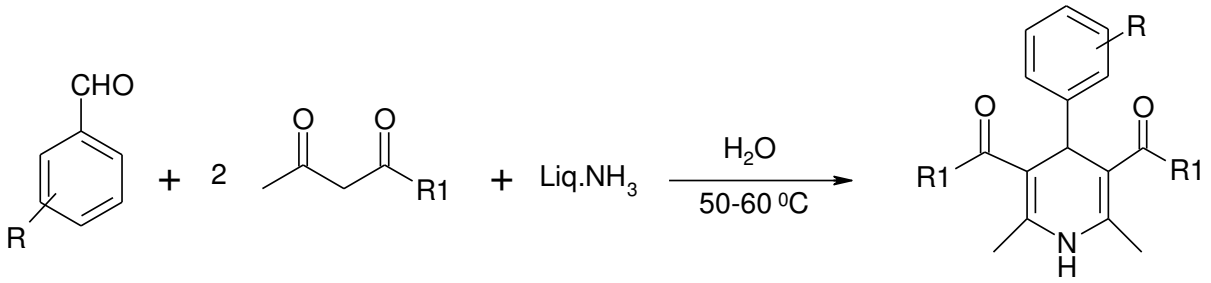
Scheme. 12 Condensation synthesis of 1,4-dihydropyrimidines under MWI

The one-pot condensation of aldehydes, acetoacetates, and ammonium acetate in ionic liquid n-butyl pyridinium tetrafluoroborate ([BPy][BF4]) produced the corresponding Hantzsch 1,4-dihydropyridines with good yields (Scheme 13) [41].



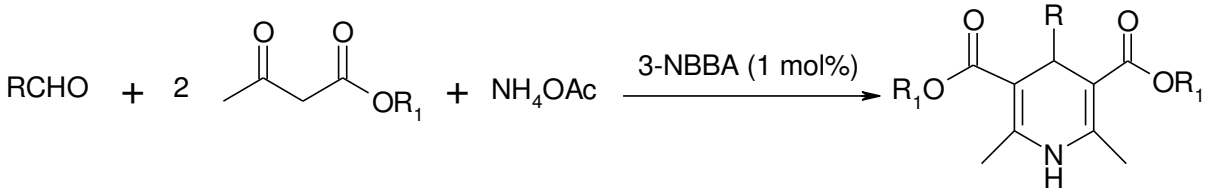
Scheme. 13 Synthesis of 1,4-dihydropyrimidines using [BPy] or [BF4] as ionic liquids

Makone et al. [42] developed an un-catalyzed and green method for the synthesis of 1,4-dihydropyridine derivatives (Scheme 14). The method consists of mixing aromatic aldehydes and β-dicarbonyl compounds in 10 mL and refluxing for 10 min to 15 min. The reaction mixture was then cooled, and liquid NH_3 was added to the reaction mixture. The reaction mixture was refluxed at 50 °C to 60 °C. This synthesis method provided the corresponding 1,4-dihydropyridines with high yields.



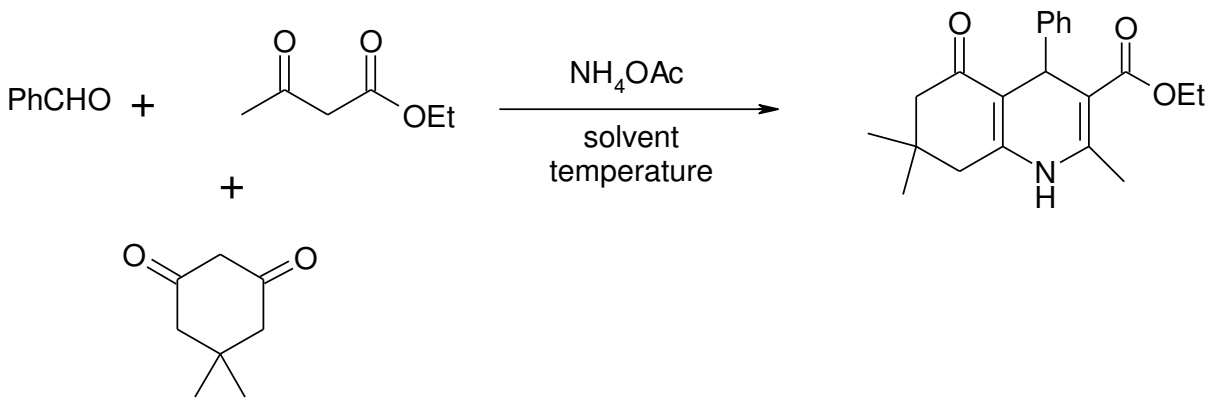
Scheme. 14 Green synthesis of 1,4-dihydropyrimidines under refluxed water

An efficient method to synthesize Hantzsch 1,4-dihydropyridines was also developed by Bhusare et al. [43] by applying 3-nitrophenylboronic acid as a catalyst for the one-pot coupling reaction of aldehyde derivatives, β-keto ester, and ammonium acetate at room temperature (Scheme 15).



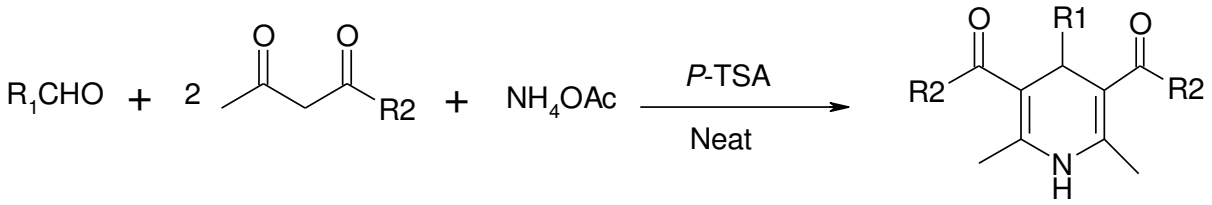
Scheme. 15 Effective synthesis of 1,4-dihydropyrimidines using 3-NBBA as catalyst

Ghadge et al. [44] further reported an efficient technique to synthesize differently substituted 1,4-dihydropyridines in deep eutectic solvents via the four-component reaction of benzaldehyde, ethyl acetoacetate, dimedone, and ammonium acetate under solvent-free conditions (Scheme 16). The synthesized products were obtained at very high yields, and minimal loss was observed in the activity of the deep eutectic solvents up to five recycles.



Scheme. 16 Four-component synthesis of 1,4-dihydropyrimidines using eutectic solvents

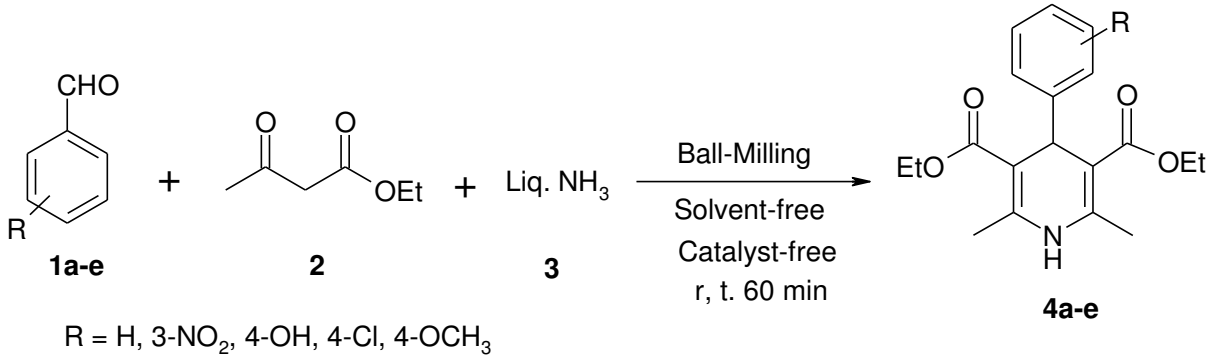
Hantzsch 1,4-dihydropyridine derivatives were synthesized via the multi-component coupling reaction of aldehydes, β-dicarbonyl compounds, and ammonium acetate for 5 min to 20 min by using *p*-toluenesulfonic acid as a catalyst without adding any solvent. All the products were synthesized with excellent yields (80%–96%) (Scheme 17) [45].



Scheme. 17 Multi-component of 1,4-dihydropyrimidines catalyzed by *P*-TSA

RESULTS AND DISCUSSION

As a continuation of our research on the applications of ball milling in organic synthesis [28], we report an eco-friendly, effective, and high-yield one-pot synthesis of Hantzsch 1,4-dihydropyrimidine derivatives. In this technique, aromatic aldehydes, ethyl acetoacetate, and ammonia are directly placed in a simple planetary ball mill under solvent- and catalyst-free conditions (Scheme 18).



Scheme . 18 One-pot synthesis of Hantzsch 1,4-dihydropyrimidines under ball milling Solvent-free catalyst-free

To optimize the conditions for the synthesis of Hantzsch 1,4-dihydropyrimidines, we placed benzaldehyde (0.01 mol), ethyl acetoacetate (0.02 mol), and ammonia (1 mL) (with a total mass of 3.26 g) in a tempered vial. We subsequently added 16.30 g of balls (ratio of the ball weight to the reagent weight is equal to 5) [28]. The progress of the reaction was monitored every 10 min of the milling cycle via thin-layer chromatography (TLC). The reaction was completed after 60 min. Similar conditions were applied to different reactions, and all the synthesized products were obtained in the same time.

The spectral data correspond to different synthesized products. Products **4a–e** (Table 1) show a characteristic single peak in the ^{1}H-NMR spectra at approximately 4.79–5.08 ppm (s, 1H). This peak corresponds to the proton of the sp^{3} carbon in the pyridine ring. The signal in the ^{13}C-NMR spectra at approximately 38.05–40.12 ppm belong to the carbone sp^{3} in the pyridine ring.

Table. 1 Synthesis of Hantzsch 1,4-dihydropyrimidines using ball milling solvent-free catalyst-free.

Entry	R	Product	Yield(%)
1	H	4a	94
2	3-NO_2	4b	96
3	4-OH	4c	92
4	4-Cl	4d	90
5	4-OCH_3	4e	91

SPECTRAL DATA

The spectroscopic data for synthesized products in this chapter are recorded in the experimental part.

We provide for example the IR spectrum of the product **4a**

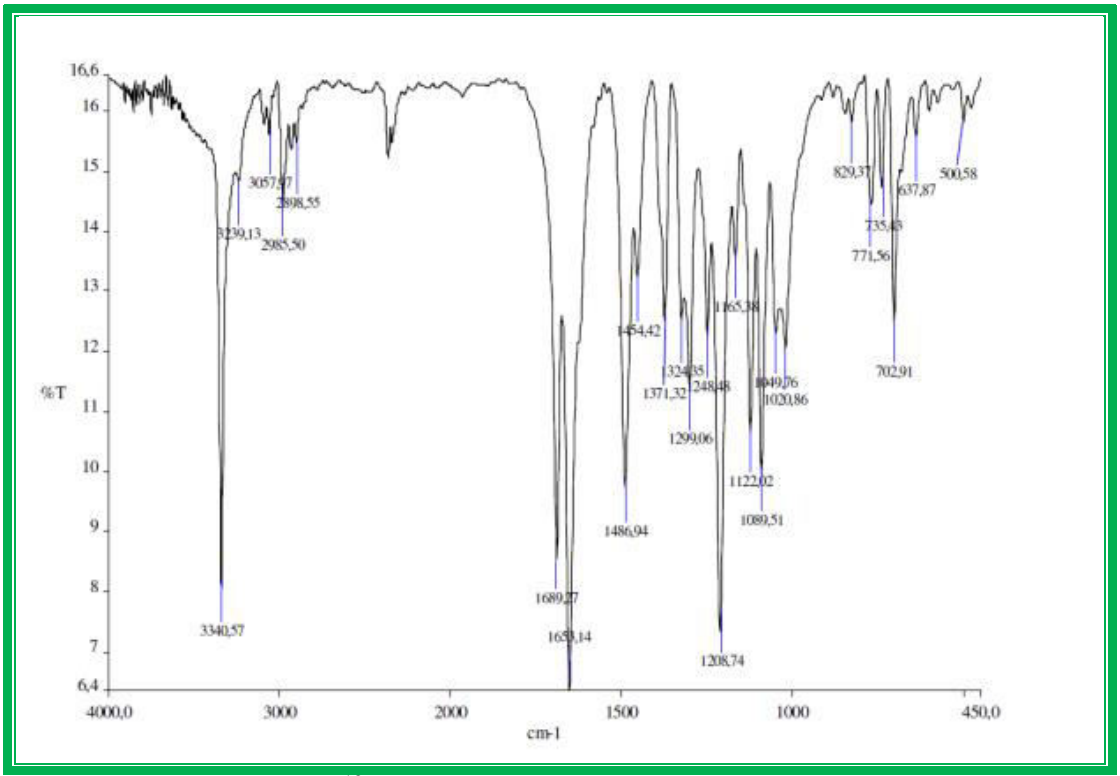


Figure I: ^{13}C NMR spectrum of compound **4a** in KBr

The 1 H NMR spectrum of the product **4a**

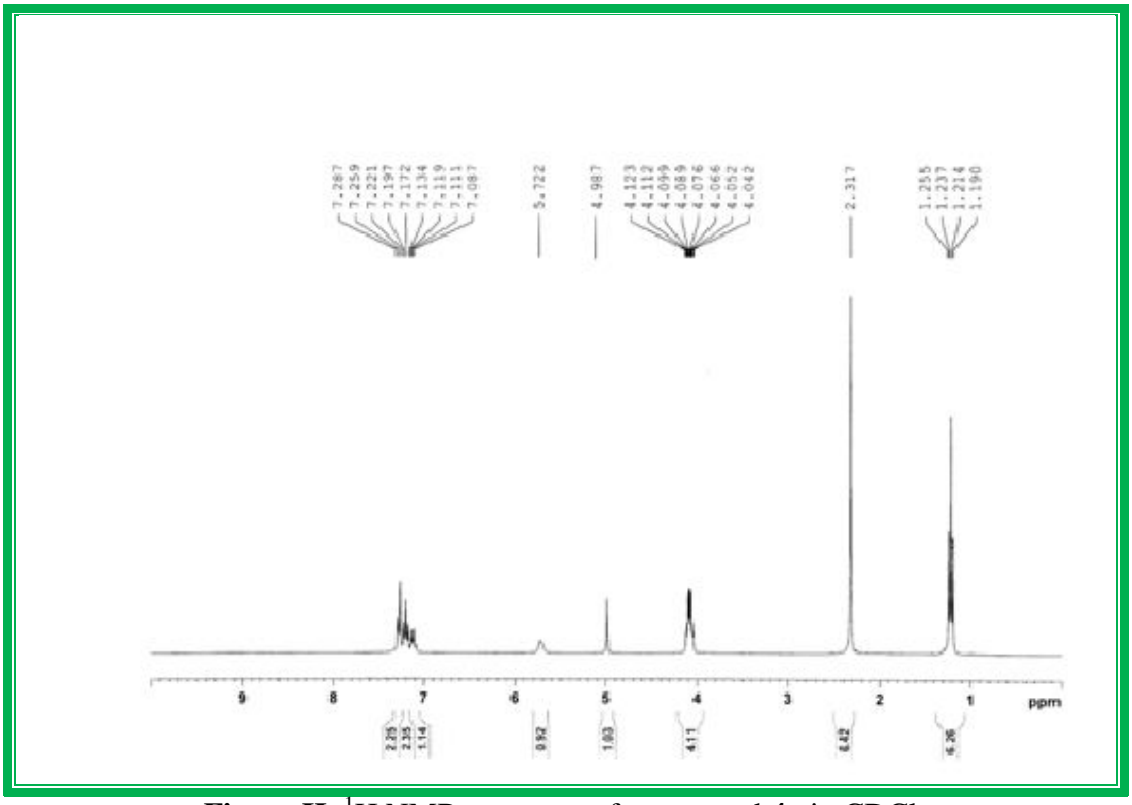


Figure II: ^{1}H NMR spectrum of compound **4a** in $CDCl_3$

The ^{13}C NMR spectrum as an example for the product **4a**

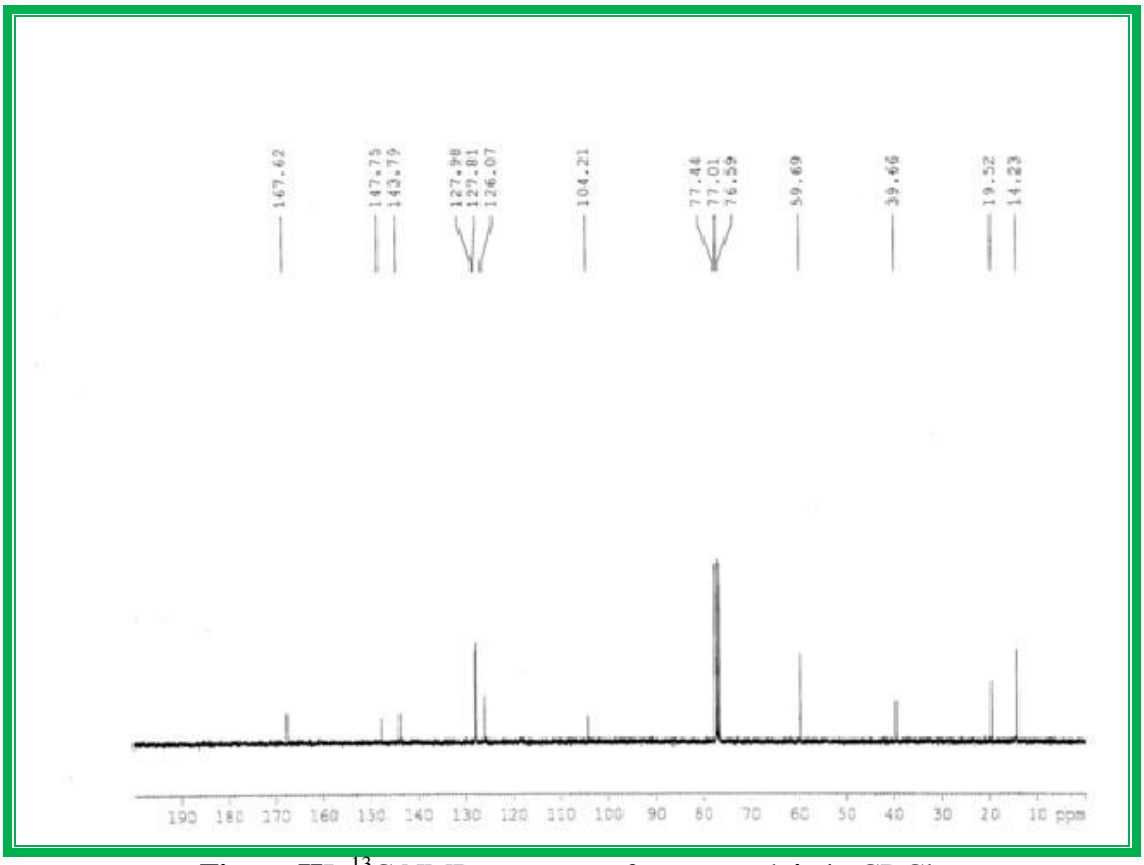


Figure III: ^{13}C NMR spectrum of compound **4a** in $CDCl_3$

CONCLUSION

We described a simple, operational, and green one-pot synthesis of Hantzsch 1,4-dihydropyrimidines (Table 1) by applying the ball milling technique. This economical and eco-friendly method can be used to synthesize all products in a short period of time and with high yields**.**

EXPERIMENTAL PART

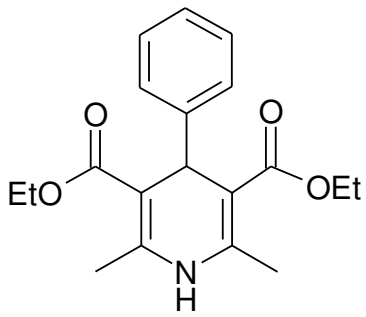
1. Materials and Techniques

The ball mill used in this study was a Planetary Micro Mill PULVERISETTE 7 classic line with 10 cm^3 stainless steel vials. Melting points were determined using the Stuart Melting point apparatus SMP10. The IR spectra were obtained using an FT-IR-Tensor 27 spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were determined using a BRUKER 300 NMR spectrometer in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed as δ ppm units. The progress of all reactions was monitored via TLC on silica gel 60 (Merck) by using a chloroform–ethanol system.

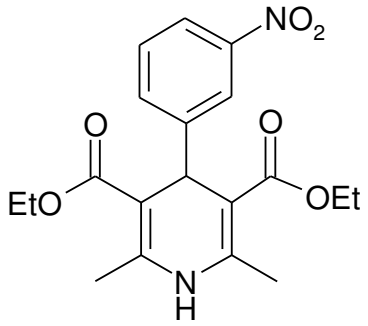
2. General Procedure for the Synthesis of Pyridine Compound 4a

A mixture of benzaldehyde (0.01 mol), ethyl acetoacetate (0.02 mol), and ammonia solution (1 mL) with a total mass equal to 3.26 g was placed in stainless steel vials with 16.30 g of stainless steel balls (12 mm in diameter). The vials were closed and then placed in a Planetary Micro Mill PULVERISETTE 7 classic line. Crude compound 4a was obtained after 60 min of milling time and purified via recrystallization in ethanol.

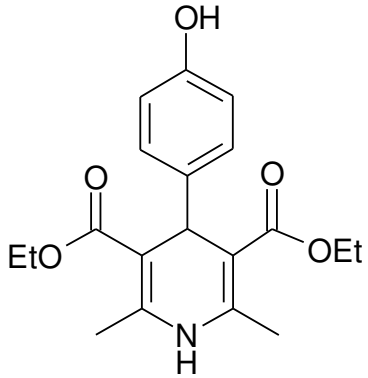
4a: Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate. M.P.:159-161 ^0C; IR (KBr): 3341, 2925, 1687, 1650, 1123, 738; 1H NMR ($CDCl_3$, 300MHz): δ 1.22(t, *J*=9.7Hz, 6H), 2.32(s, 6H), 4.06 (q, *J*=6Hz, 2H), 4.11(q, *J*=6.3Hz, 2H), 4.99(s, 1H), 5.72(s, 1H), 7.09-7.29 (m, 5H); 13C NMR ($CDCl_3$, 75MHz): δ 14.23, 19.52, 39.66, 59.69, 104.21, 126.07, 127.81, 127.98, 143.79, 145.75, 167.62.



4b: Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. M.P.: 176-178 ^{o}C; IR (KBr): 3323, 2923, 1698, 1672, 1459, 1376, 1117, 786; 1H NMR ($CDCl_3$, 300MHz): δ 1.20(t, *J*=7.4Hz, 6H), 2.35(s, 6H), 4.06(q, *J*=8.4Hz, 2H), 4.10(q, *J*=8.7Hz, 2H), 5.08(s, 1H), 5.88(s, 1H), 7.36(t, *J*=7.9Hz, 1H), 7.63(d, *J*=7.8Hz, 1H,), 7.99(d, *J*=8.1Hz, 1H), 8.11(s, 1H); 13C NMR ($CDCl_3$, 75MHz): δ 14.19, 19.57, 39.94, 59.95, 103.32, 121.29, 123.08, 128.55, 134.47, 144.67, 148.14, 149.88, 167.08.

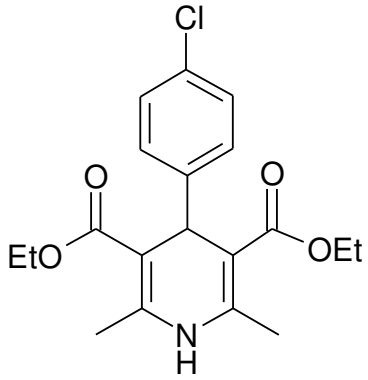


4c: Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarboxylate. M.P.: 241-243 ^{o}C ; IR (KBr): 1H NMR (CDCl3, 300MHz): δ 1.19(t, *J*=7.2Hz, 6H), 2.30(s, 6H), 4.03(q, *J*=6.6Hz, 2H), 4.08(q, *J*=6.3Hz, 2H), 4.89(s, 1H), 5.56(s, 1H), 6.63(d, *J*=8.7Hz, 2H), 7.10(d, *J*=8.4Hz, 2H), 9.84(s, 1H) ; 13C NMR ($CDCl_3$, 75 MHz): δ 13.85, 18.49, 38.05, 58.86, 103.11, 114.23, 128.40, 139.09, 144.17, 154.81, 167.51.

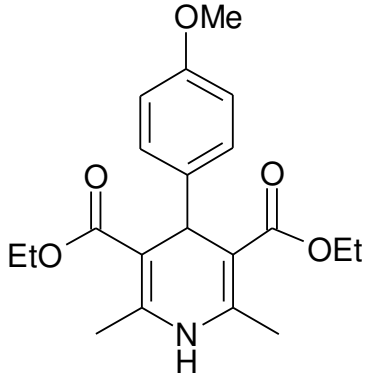


4d: Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. M.P.: 156-157 ^{o}C; IR (KBr): 3358, 2987, 1695, 1651, 1118, 831; 1H NMR ($CDCl_3$, 300

MHz): δ 1.08(t, *J*=7.1Hz, 6H), 2.21(s, 6H), 3.94(q, *J*=8.7Hz, 4H), 4.79(s, 1H), 7.11(d, *J*=8.4Hz, 2H), 7.21(d, J=8.1Hz, 2H), 8.81(s, 1H); 13C NMR ($CDCl_3$, 75 MHz): δ 14.25, 18.32, 40.12. 59.17, 101.59,117.80, 127.91, 129.31, 130.51, 145.74, 147.20, 166.85.



4e: Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarboxylate. M.P. : 161-163 ^oC ; IR (KBr): 1H NMR (CDCl3, 300MHz): δ 1.22(t, *J*=7.0Hz, 6H), 2.32(s, 6H), 3.75(s, 3H), 4.06(q, *J*=6.3Hz, 2H), 4.11(q, *J*=6.6Hz, 2H), 4.92(s, 1H), 5.61(s, 1H), 6.75(d, *J*=8.4Hz, 2H), 7.18(d, *J*=8.7Hz, ,2H); 13C NMR ($CDCl_3$, 75MHz): δ 14.27, 19.58, 38.76, 55.14, 59.68, 104.45, 113.20, 128.95, 140.32, 143.47, 157.90, 167.67.



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