An Efficient One-Step Hantzsch Multicomponent Synthesis of 1,4-Dihydropyridines *Via* a Wells-Dawson Heteropolyacid Catalyst Under Solvent-Free Conditions

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Abstract: In this work, we report the use of bulk Wells-Dawson acid ($H_6P_2W_{18}O_{62}.24H_2O$) as a reusable, heterogeneous catalyst to obtain substituted 1,4-dihydropyridines for the Hantzsch multicomponent reaction, using various aldehydes, alkyl acetylacetates and ammonium acetate or aniline as source of ammonia. The reaction experiments were performed in the absence of solvent, at 80°C. Under these conditions fourteen examples were obtained with very good yields (90-98%) and high selectivity. The catalyst was easily recycled and reused without appreciable loss of their catalytic activity. The synthetic method presented is a simple, clean and environmentally friendly alternative for obtaining substituted dihydropyridines.

Keywords: Wells-Dawson, dihydropyridines, multicomponent reactions, acid catalysis.

INTRODUCTION

In recent years, considerable attention has been paid to the synthesis of 1,4-dihydropyridines (1,4-DHPs) owing to their significant biological activity [1-5]. They can cure the disordered heart ratio as a chain-cutting agent of factor IV channel, undergo the calcium channel agonist–antagonist modulation activities [6,7] and also behave as neuroprotective agents and chemosensitizers [8]. Furthermore, the dihydropyridine skeleton is common in many bronchodilator, antitumor, antidiabetic, and hepatoprotective agents [9-11]. They also function as neuroprotectants, and are important in Alzheimer's disease as anti-ischemic agents [8,12]. Among 1,4-DHPs, there are also examples of drug-resistance modifiers [13], antioxidants [14] and a drug for the treatment of urinary urge incontinence [15]. Some biological relevant examples of 1,4-DHPs are shown in Fig. (**1**).

The classical methods involve the three-component condensation of an aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol [16-18].

Several methods are reported for this synthesis, such as those employing microwaves [19], infrared irradiation [20], molecular iodine [21], cyanuric chloride [22], ionic liquids [23], silica gel/$NaHSO_4$ [24], TMSCl–NaI [25], metal triflates [26], heteropolyacids [27,28] and solvent-free conditions using different catalysts as well as activated fly ash, an industrial waste [29,30]. Recently Ghorbani-Choghamarani and coworkers reported an important procedure under solvent-free conditions and in the absence

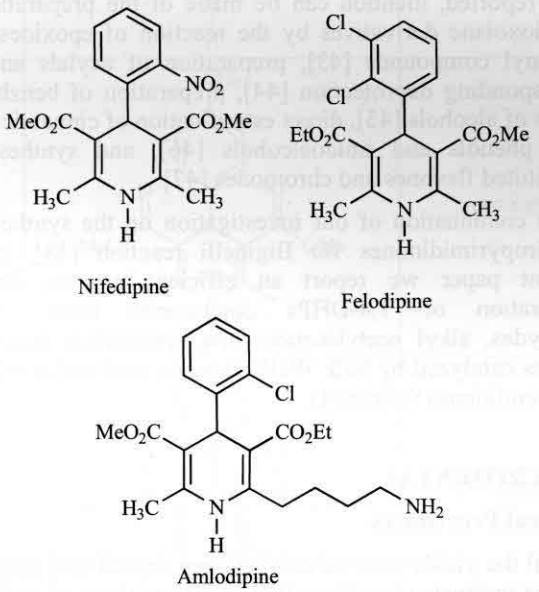

Fig. (1). Bioactive dihydropyridines.

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of a catalyst [31] in which 1,4-dihydropyridine derivatives were achieved *via* condensation of methyl acetoacetate or ethyl propiolate with various alkyl and aryl aldehydes and ammonium acetate at 80 °C.

But some of these methods still have their own limitation in terms of yields, longer reaction time, and difficult work-up. In some cases, the catalysts used are harmful to the environment and cannot be reused. Therefore, a novel method for the preparation of dihydropyrimidine derivatives is still desired.

On the other hand, there is an increasing interest in the area of heteropolycompound-induced organic transformations. In view of their remarkable catalytic properties, heteropolycompounds are applied both in bulk or supported form. For a long time, our efforts were focused on the development of environmentally benign synthetic methods using supported heteropolyacids (HPA) [32-34].

The molecular structure of the Wells-Dawson (WD) heteropolyacid catalyst ($H_6P_2W_{18}O_{62}.24\ H_2O$) [35,36] shows two identical "half units" PW_9 linked through the oxygen atoms, and consists of a close-packed framework of W(VI)-oxygen WO_6 octahedra surrounding a central P(V) atom. Wells-Dawson HPA has been reported as a useful catalyst for the sustainable synthesis of various organic compounds, for example 1,1,3-trimethyl-3-phenylindan [37], 4-substituted 1,3-dioxanes [38] and coumarins [39]. Several reviews including this matter have been published recently [40-42]. Over the last years, WD-catalyzed reactions have been reported, mention can be made of the preparation of 1,3-dioxolane derivatives by the reaction of epoxides with carbonyl compounds [43], preparation of acylals and the corresponding deprotection [44], preparation of benzhydryl ethers of alcohols [45], direct esterification of cinnamic acids with phenols and imidoalcohols [46], and synthesis of substituted flavones and chromones [47].

In continuation of our investigation on the synthesis of dihydropyrimidinones *via* Biginelli reaction [48], in the present paper we report an efficient process for the preparation of 1,4-DHPs compounds from various aldehydes, alkyl acetylacetates and ammonium acetate or amines catalyzed by bulk Wells-Dawson acid under solvent-free conditions (Scheme **1**).

EXPERIMENTAL

General Procedures

All the yields were calculated from crystallized products. All the products were identified by comparison of analytical data, melting point (mp), thin layer chromatography (TLC), nuclear magnetic resonance (NMR); with those reported or with authentic samples prepared by the conventional method using sulfuric acid as catalyst. All the starting materials are commercial products. Melting points of the compounds were determined in open capillary tubes and are uncorrected. ^{13}C NMR and ^{1}H NMR spectra were recorded at room temperature on Bruker AC-200 using tetramethylsilane (TMS) as internal standard.

Catalyst Preparation

The Dawson acid ($H_6P_2W_{18}O_{62}.24H_2O$) was prepared by the Drechsel method [35] from an α/β $K_6P_2W_{18}O_{62}.10\ H_2O$ isomer mixture. This Dawson-type salt was prepared according to the technique reported by Lyon *et al.* [49]. Concentrated H_3PO_4 in a 4:1 acid/salt ratio was added to a boiling aqueous solution of $Na_2WO_4.2H_2O$, and the mixture was kept boiling in a reflux system for 8 h. The salt was precipitated by adding KCl, then purified by recrystallization and cooled overnight to 278 K. The product, which is a mixture of the α and β isomers, was filtered, washed and then vacuum-dried for 8 h.

The acid was obtained from an aqueous solution of α/β $K_6P_2W_{18}O_{62}.10H_2O$ salt, which was treated with ether and concentrated HCl (37%) solution. The Dawson acid so released formed an additional compound with the ether, which was separated from the solution. After obtaining the ether solution with the acid, ether was eliminated by flowing dry air, and the remaining solution was placed in a vacuum-desiccator until crystallization.

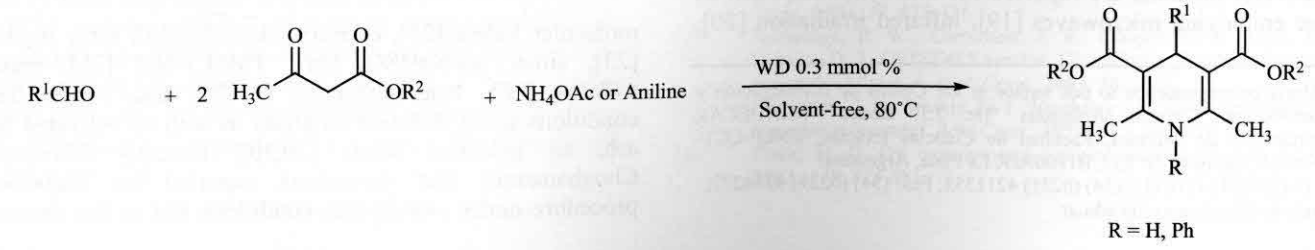
General Procedures for the Preparation of Substituted Dihydropyrimidines

The solid catalyst (0.3 mmol %) was added to a mixture of aldehyde (1 mmol), alkyl acetylacetates (2.5 mmol) and ammonium acetate or aniline (1.5 mmol). The mixture was stirred at 80°C for the indicated time (Table **1**). The progress of the reaction was monitored by TLC. After completion of the reaction, hot toluene was added (2 x 2 mL) and the catalyst was filtered. The extracts were combined and dried with anhydrous sodium sulfate and concentrated in vacuum. All the solid crude products were recrystallized.

NMR spectra of the representative compounds:

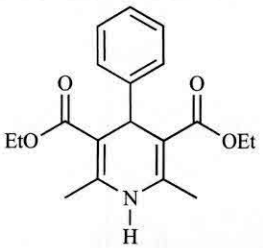
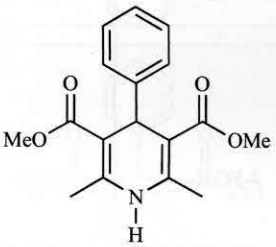
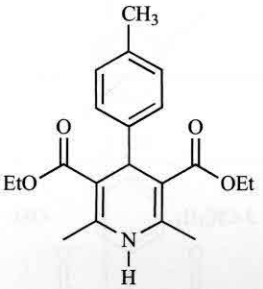
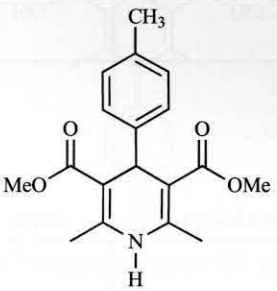
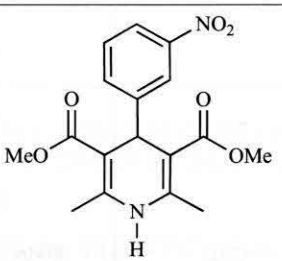
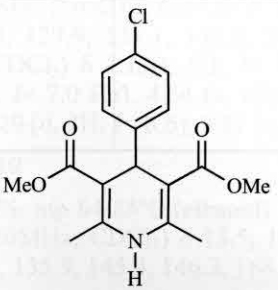
Compound 1

Yield 96%, mp: 157-158°C (ethanol) (lit. mp: 156-158°C) [50], ^{13}C NMR (50MHz, $CDCl_3$) δ 14.8, 18.9, 39.5, 59.7, 102.5, 126.5, 128.0, 128.5, 146.0, 148.8, 167.6; ^{1}H NMR

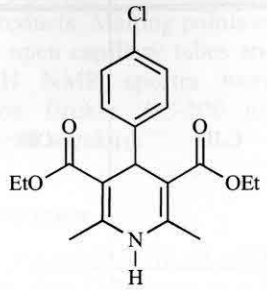
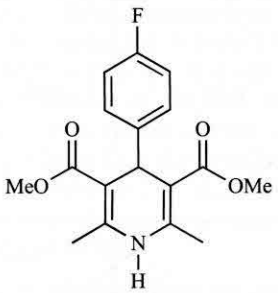
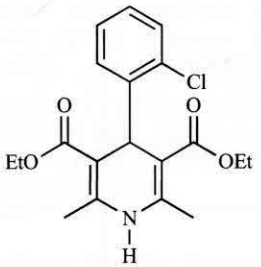
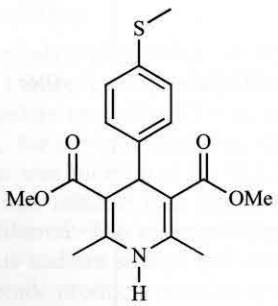
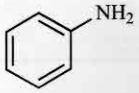
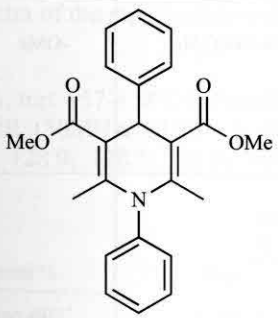


Scheme 1.

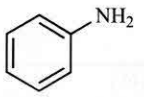
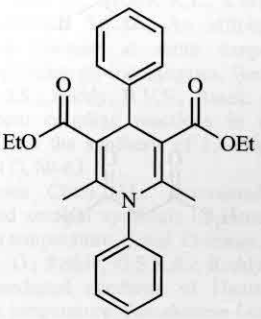
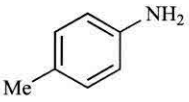
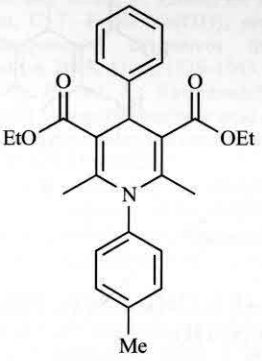
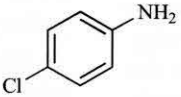
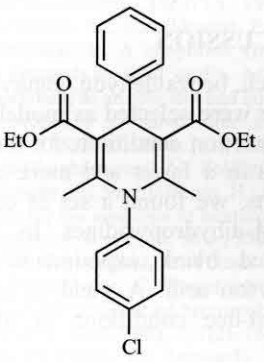
Table 1. Hantzsch Synthesis of Dihydropyridines[a]

Entry	R^1	R^2	NH_4OAc or Aniline	Product[b]	Time (min)/yields (%)[c]/TOF[d]
1	C_6H_5	-OEt	NH_4OAc		30/96 (94,93)[e]/640 (627,620)
2	C_6H_5	-OMe	NH_4OAc		25/95/754
3	4-MeC_6H_4	-OEt	NH4OAc		30/98/653
4	4-MeC_6H_4	-OMe	NH_4OAc		30/97/647
5	3-$NO_2C_6H_4$	-OMe	NH_4OAc		35/92/529
6	4-ClC_6H_4	-OMe	NH_4OAc		30/93/620

(Table 1). Contd.....

Entry	R^1	R^2	NH_4OAc or Aniline	Product[b]	Time (min)/yields (%)[c]/TOF[d]
7	4-ClC_6H_4	-OEt	NH_4OAc		30/98/653
8	4-FC_6H_4	-OMe	NH_4OAc		45/93/413
9	2-ClC_6H_4	-OEt	NH_4OAc		80/94/236
10	4-$MeSC_6H_4$	-OMe	NH_4OAc		40/96/478
11	C_6H_5	-OMe			120/90/150

(Table 1). Contd.....

Entry	R^1	R^2	NH_4OAc or Aniline	Product[b]	Time (min)/yields (%)[c]/TOF[d]
12	C_6H_5	-OEt			120/90/150 (480/71/30)[f]
13	C_6H_5	-OEt			120/87/145
14	C_6H_5	-OEt			120/84/140

[a]Reaction conditions: aldehyde: 1 mmol, β-ketoester: 2.5 mmol, ammonium acetate or aniline: 1.5 mmol; catalyst: 0.3 % mmol; temperature: 80ºC; solvent-free conditions.
[b]All productos were characterized by C^{13}-H^1 RMN spectroscopic data and compared with literature.
[c]Yields of recrystallized product.
[d]Turnover frequency (product mols x WD mols $^{-1}$ x h $^{-1}$).
[e]Yield after a second and third run.
[f]Without catalyst.

(200MHz, $CDCl_3$) δ 1.13 (t 6H, J= 7.0 Hz), 2.26 (s, 6H), 3.98 (q, 4H, J= 7.0 Hz), 4.86 (s, 1H), 7.12-7.21 (m, 5H), 8.81 (s, 1H).

Compound 2

Yield 95%, mp: 195-197ºC (ethanol) (lit. mp: 196-197ºC) [31], ^{13}C NMR (50MHz, $CDCl_3$) δ 19.6, 39.3, 51.0, 103.9, 126.2, 127.6, 128.0, 144.2, 147.4, 168.0; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.34 (s, 6H), 3.64 (s, 6H), 5.01 (s, 1H), 8.75 (s, 1H), 7.13-7.26 (m, 5H).

Compound 6

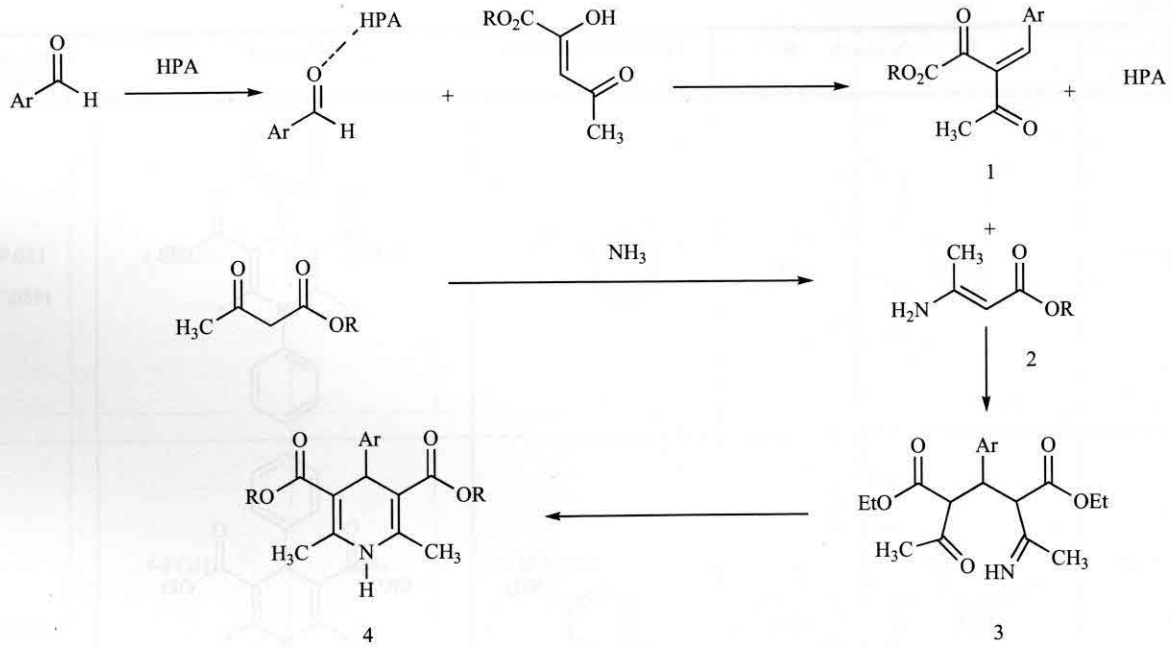
Yield 93%, mp 197-198ºC (ethanol) (lit. mp: 196-198ºC) [51], ^{13}C NMR (50MHz, $CDCl_3$) δ 18.9, 38.9, 51.4, 101.8, 128.7, 129.6, 131.2, 146.7, 147.4, 167.9; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.26 (s, 6H), 3.54 (s, 6H), 4.87 (s, 1H), 7.12-7.16 (d, 2H, J= 8.3), 7.25-7.29 (d, 2H, J= 8.3), 8.96 (s, 1H).

Compound 7

Yield 98%, mp 145-147ºC (ethanol) (lit mp: 147-148ºC) [50], ^{13}C NMR (50MHz, $CDCl_3$) δ 14.8, 18.9, 39.2, 59.8, 102.1, 128.5, 129.9, 131.1, 146.3, 147.8, 167.4; ^{1}H NMR (200MHz, $CDCl_3$) δ 1.13(t, 6H, J= 7.0 Hz), 2.26 (s, 6H), 3.90 (q, 4H, J= 7.0 Hz), 4.84 (s, 1H), 7.13-7.18 (d, 2H, J= 8.6), 7.25-7.29 (d, 2H, J= 8.6), 8.87 (s, 1H).

Compound 10

Yield 94%, mp 84-85ºC (ethanol) (lit mp: 83-85ºC) [52], ^{13}C NMR (50MHz, $CDCl_3$) δ 15.5, 18.9, 38.7, 51.3, 102.1, 126.6, 128.3, 135.9, 145.4, 146.3, 168.0; ^{1}H NMR (200MHz,



Scheme 2. Proposal mechanism.

$CDCl_3$) 2.25 (s, 6H), 2.41 (s, 3H), 3.54 (s, 6H), 4.83 (s, 1H), 7.08-7.11 (m, 4H), 8.87 (s, 1H).

RESULTS AND DISCUSSION

In our initial research, benzaldehyde, methyl acetoacetate and ammonium acetate were selected as model substrates in order to optimize the reaction conditions for the synthesis of 1,4-dihydropyrimidines in a faster and more efficient way. After some experiments, we found a set of conditions that generally provide 1,4-dihydropyridines in good yields. Initially, we conducted blank experiments without the presence of Wells-Dawson acid. A yield of only 76% was detected under solvent-free conditions at 80°C for 120 minutes.

Afterwards the catalytic activity of the bulk Wells-Dawson acid (WD) was tested in the preparation of different 1,4-dihydropyridines. The obtained results are shown in Table **1**. The experiments were carried out under solvent-free conditions, in the presence of 0.3% mmol catalyst. Temperature and molar ratio of the Wells-Dawson acid to substrates were checked to optimize the reaction. The use of just 0.3% mmol of HPA is enough to push the reaction forward; higher amounts of the catalyst did not improve the results. The reactions were completed within 15-30 minutes at 80°C, and the crude products were obtained by simple filtration of the catalyst and evaporation of the hot toluene solution of product.

The experiments were run until substrates were consumed or until no changes in the composition of the reaction mixture were observed (TLC). In all the cases, the desired products were obtained with high selectivity, almost free of secondary products. Recycling of catalyst (Table **1**, Entry 1) was checked in two consecutive batches after the first one; the catalysts showed almost constant activity. However, the experiments performed under solvent-free conditions showed a substantial reduction of the reaction times. No stereoelectronic effects owing to the substituent were observed on the yield, for each of the catalysts.

To examine the versatility of the reaction, the preparation of two 1,4-DHPs was tested using aniline as a source of ammonia. The reactions were completed in 120 minutes at 80°C, and the yields of both 1,4-DHPs were 90% (Table **1**, entries 11 and 12).

From a mechanistic point of view, the first step of this reaction can be visualized as the Bronsted Wells-Dawson heteropolyacid-catalyzed formation of Knoevenagel product 1. A second key intermediate is enaminoester 2, produced by condensation of the second equivalent of the β-ketoester with ammonia. Condensation of these two fragments gives intermediate 3, which subsequently cyclizes to 1,4,-dihydropyridine 4 (Scheme **2**).

CONCLUSIONS

The procedure described above provides a clean, simple and useful alternative for preparing substituted dihydropyrimidines. The use of WD catalyst provides very good yields, also leading to an easy separation and recovery of the catalysts for further use. The catalytic activity is practically constant in two more consecutive reaction batches, and the procedure is of low cost. Other advantages of the method are the low formation of wastes and the replacement of corrosive soluble mineral acids.

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