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TUNGSTOPHOSPHORIC ACID SUPPORTED ON TITANIA AS AN ECO-FRIENDLY, GREEN AND REUSABLE CATALYST FOR THE SOLVENT-FREE HANTZSCH MULTI-COMPONENT CONDENSATION

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Abstract – Tungstophosphoric acid supported on titania (PW/TiO_2), catalyzed three and four component coupling of various β-dicarbonyl compounds, aldehydes and amines under solvent free conditions. Different 4-aryl, N-hydroxy ethyl and N-aryl substituted 1, 4-dihydropyridines and polyhydroquinoline derivatives, have been synthesized with high to excellent yields. Short reaction times, simple work-up, and mild reaction conditions are advantages of this procedure. The catalyst is reusable without loss of activity for five runs.

INTRODUCTION

At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials.[1] Green chemistry approach hold out significant potential not only for reduction of by products, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies.[2] Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/ product ratio , are perhaps the most ripe for greening.[3]

In the main stream of the current interest in one-pot multicomponent reactions[4] that permit a rapid access to combinatorial libraries of organic molecules for efficient lead structure identification and optimization in drug discovery,[5,6] the acid-catalyzed condensation of aldehyde, β-ketoester, and ammonia, known as the Hantzsch reaction from the name of its inventor,[7] is receiving increased attention. This reaction generated multi functionalized products including 1, 4-dihydropyridines (1, 4-DHP), polyhydroquinolines derivatives and other related heterocyclic compounds. Five- and six-membered heterocyclic compounds are important constituents that often exist in biologically active natural products and synthetic compounds

of medicinal interest. 4-Aryl-1, 4-DHPs are analogues of NADH coenzymes which have been explored for their calcium channel activity.[8] Cardiovascular agents such as nifedipine, amlodipine, felodipine, nimodipine (Figure 1) and other related derivatives are dihydropyridyl compounds which are effective for the treatment of angina and hypertension.[9]

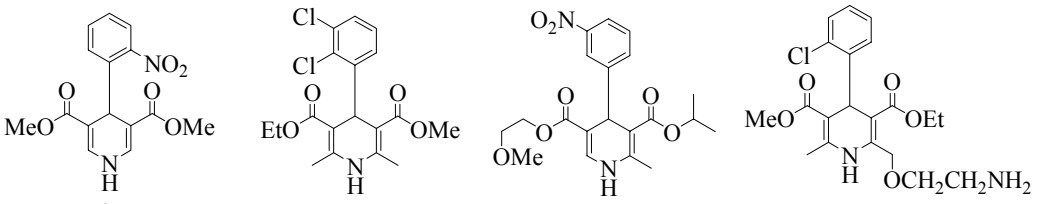


Figure 1. Typical medicinal 1, 4-DHPs

These compounds exhibit various medicinal functions such as neuroprotectant, platelet anti-aggregatory activity, chemosensitizer in tumor therapy and cerebral antischemic activity in the treatment of Alzheimer's disease.[10-13] Moreover, they serve as key intermediates in biogenesis of indol alkaloids[14,15] and participate actively in biochemical oxidoreductase and transaminase reactions.[16] These examples clearly indicates the remarkable potential of 1, 4-DHP derivatives as a source of valuable drug units.

The classical method for the synthesis of these compounds, suffer from several disadvantages such as long reaction times, poor yields, harsh reaction conditions and use of large quantities of volatile organic solvents. Thus, a number of modified methods under improved conditions have been reported.[17-31] However, unsatisfactory yields, high temperatures, expensive metal precursors, use of hazardous solvents and non recyclable or reused catalysts limit the use of some of these procedures. Additionally, since the classical approach yielding *N*-alkyl or *N*-aryl 1, 4-DHPs derivatives with negative results or very poor yields, most of these studies have been devoted to Hantzsch synthesis of *N*-unsubstituted DHPs. Modified synthetic methodologies for *N*-substituted 1, 4-DHPs reportly provided improve yields, but used expensive reagents or high temperatures and required long reaction times.[32,33] Hence, the development of simple procedure by using of reusable catalyst and solvent free condition is of prime importance.

The strong Brönsted acidity[34,35] of heteropolyacids (HPAs) and the softness of the heteropoly anions are responsible for their high catalytic activities in the reactions.[36] In comparison with the conventional liquid acid catalysts, HPAs have advantages of being non-corrosive, environmentally benign, and presenting fewer disposal problems. Due to the more reactivity of these compounds than conventional inorganic and organic acids, they have found interesting industrial applications in synthesis of antioxidants, medicinal preparations, vitamins, and biologically active substance and some are already applied in practice.[37-40] Another crucial point is the chemical stability and also, it should be anchored to physically robust framework in order to secure recovery without detriment of catalytic properties. The main disadvantage

of HPAs as catalysts is their very low surface area (< 10 m^2g^{-1}) and thus, it becomes necessary to disperse them on supports that possess large surface area. Several supports such as silica, alumina, clays, carbon and titania have been used to enhance the dispersion of HPA, thereby increasing the accessibility to their acidic sites. Among them, titania is known to enhance the activity in many cases due to the strong interaction between the active phase and the supports.[41]

In view of the biological importance of 1, 4-DHPs and in continuation of our attempt toward "Green" synthesis,[42-44] this paper describes the improvement of one-pot symmetrical and unsymmetrical Hantzsch reactions using PW/TiO_2 as a reusable and non-toxic catalyst under solventless conditions.

RESULTS AND DISCUSSION

At first the three component condensation reaction of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1 mmol) was performed in the presence of catalytic amount of several supported HPAs (Table 1). Various supported HPAs accelerated the reaction but PW/TiO_2 gave superior results in term of yield and reaction time (Table 1, entries 1-14). With this optimistic results in hand, further investigations were done by using various quantities and different weight percent of PW (Table 1, entries 14-18). Increasing of the quantity of catalyst from 2 mol% to 3 mol%, leads to the formation of side product. Similar result was obtained when PW loading on support was increased. Thus, 2 mol% (based on aldehyde) of 40% PW/TiO_2 was selected as optimized reaction condition to exam the universality of catalyst's application.

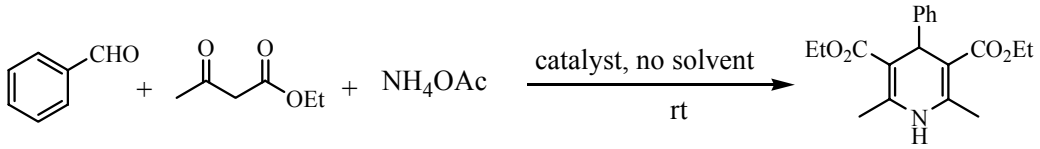
Aromatic, heterocyclic and unsaturated aldehydes react with ethyl acetoacetate and ammonium acetate in the presence of PW/TiO_2 and the corresponding products were obtained in excellent yields (Table 2, entries 1-6). However, acetophenone afforded relevant lower yield (entry 7). Bioactive *N*-substituted 1, 4-DHPs were prepared with good yields (entries 8-12). These compounds containing reactive functionalities for further manipulation of 1, 4-DHP moieties, for example, synthesis of *N*-hydroxyethyl 1, 4-DHPs (**1h, 1i**) and its bis analogous (**1j**), let us achieving to the designed new complex molecules with multi 1, 4-DHP moieties in future.[32] *N*-aryl-5, 6-unsubstituted dihydropyridines (**1k, 1l**) are also important from a synthetic point of view, since the presence of a C_5-C_6-unsubstituted bond enables the use of these compounds as enamine-like reagents, allowing the preparation of a variety of complex heterocyclic frame-works.[33]

Based on these observations, catalytic efficiency of PW/TiO_2 in the unsymmetrical Hantzsch reaction has been studied. The model reaction was carried out by mixing of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate in the presence of PW/TiO_2 at rt and corresponding product was obtained with 24% yield. Whereas by increased the temperature to 80 ºC, a significant improvement was observed and the yield of the product was increased to 95% after 15 min (Table 3,

entries 1, 2). Encouraged by these results, study was continued by using various aldehydes in the presence of the catalyst at 80 ºC. Aliphatic, aromatic and heterocyclic aldehydes afforded the polyhydroquinolines in excellent yields at short reaction times (Table 3, entries 2-8).

To the best of our knowledge, there is no report in the literature to introduce PW/TiO_2 as a reusable catalyst. When the reaction was carried out in acetonitrile as solvent, analysis of the reaction crud indicates a leaching of 90% of the PW. But in solventless conditions PW/TiO_2 could be recovered and subsequently reused several times. It showed no loss of activity after five successive runs, the yield of the product for model reaction remained 90% after fifth run.

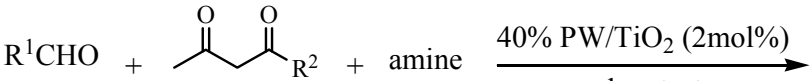
Table 1. Effect of different catalysts for condensation of benzaldehyde, ethyl acetoacetate and ammonium acetate

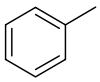
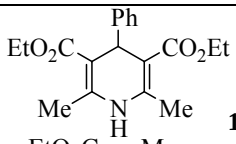
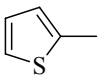
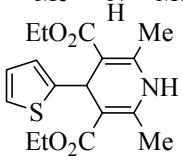
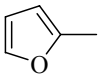
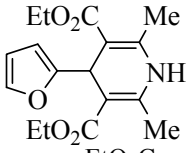
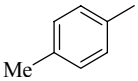
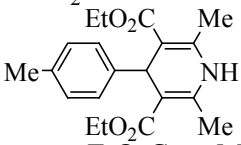
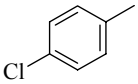
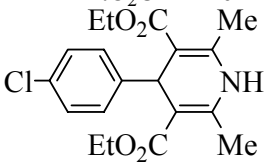
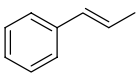
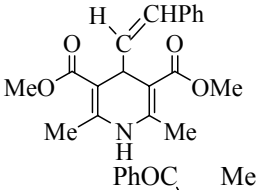
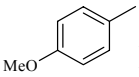
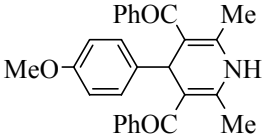
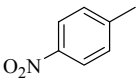
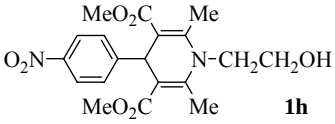
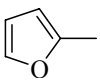
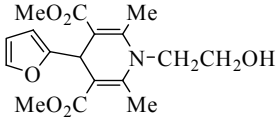
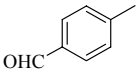
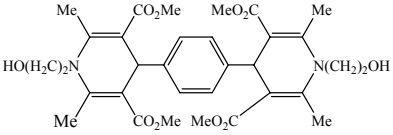


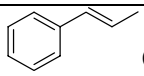
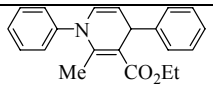
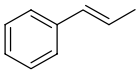
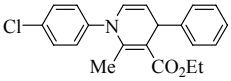
Entry	Catalyst	Time (min)	Yield (%)[a]
1	40 wt.%PW/K10 (2mol %)	11	79
2	40 wt.%PMo/K10 (2mol %)	10	80
3	40 wt.%SiW/K10 (2mol %)	15	91
4	40 wt.%PW/KSF (2mol %)	16	95
5	40 wt.%PMo/KSF (2mol %)	20	94
6	40 wt.%SiW/KSF (2mol %)	20	96
7	40 wt.%PW/γ-Al_2O_3 (2mol %)	20	92
8	40 wt.%PMo/γ-Al_2O_3 (2mol %)	20	91
9	40 wt.%SiW/γ-Al_2O_3 (2mol %)	25	70
10	40 wt.%PW/C (2mol %)	20	58
11	40 wt.%PMo/C (2mol %)	25	59
12	40 wt.% SiW/C (2mol %)	30	52
13	40 wt.% PMo/TiO_2 (2mol %)	7	61
14	40 wt.% PW/TiO_2 (2mol %)	5	92
15	20 wt.%PW/TiO_2 (2mol %)	8	63
16	60 wt.%PW/TiO_2 (2mol %)	10	44
17	40 wt.%PW/TiO_2 (1.4mol %)	11	88
18	40 wt.%PW/TiO_2 (3mol %)	10	91

[a]Isolated yield.

Table 2. TiO_2-supported $H_3PW_{12}O_{40}$ catalyzed synthesis of Hantzsch products

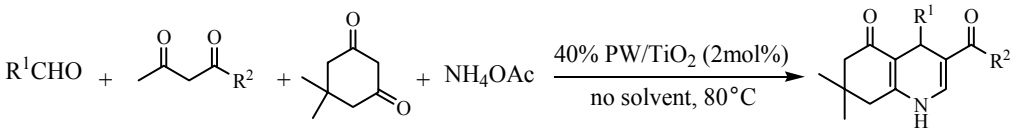


Entry	R^1	R^2	Amine	Product	Time (min) / Yield (%)	Ref
1		OEt	NH_4OAc	 **1a**	5/92	28
2		OEt	NH_4OAc	 **1b**	22/96	28
3		OEt	NH_4OAc	 **1c**	11/81	25
4		OEt	NH_4OAc	 **1d**	28/94	28
5		OEt	NH_4OAc	 **1e**	15/82	25
6		OMe	NH_4OAc	 **1f**	12/93	28
7		Ph	NH_4OAc	 **1g**	15/63	28
8		OMe	$HO(CH_2)_2NH_2$	 **1h**	27/71	32
9		OMe	$HO(CH_2)_2NH_2$	 **1i**	12/98	32
10		OMe	$HO(CH_2)_2NH_2$	 **1j**	28/86	32

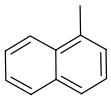
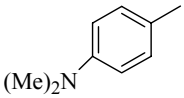
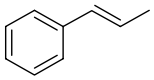
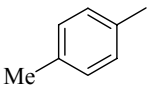
11		OEt	$PhNH_2$	 **1k**	35/63	33
12		OEt	4-Cl-$PhNH_2$	 **1l**	30/62	33

[a]Isolated yield.

Table 3. TiO_2-supported $H_3PW_{12}O_{40}$ catalyzed synthesis of polyhydroquinoline derivatives



2a-h

Entry	R^1	R^2	Product	Time (min)	Yield (%)[a]	Ref
1[b]		OEt	**2a**	60	24	27
2		OEt	**2b**	15	95	27
3		OEt	**2c**	6	92	21
4		OEt	**2d**	4	98	27
5		OEt	**2e**	3	98	27
6		OEt	**2f**	5	98	21
7	*n*-$MeCH_2CH_2$	OEt	**2g**	20	89	21
8		OMe	**2h**	12	91	27

[a]Isolated yield. [b]This reaction was performed at rt.

In summary, we have described a simple, rapid and versatile catalytic method for the synthesis of various Hantzsch products in high to excellent yields. In addition, it is possible to apply the tents of "Green Chemistry" to the generated of biologically interesting Hantzsch products using solvent less medium approach that are less expensive and non-hazardous than those with organic solvents. Recycability of supported catalyst is the main feature of this procedure.

EXPERIMENTAL

MATERIALS AND METHODS

$H_3PW_{12}O_{40}$, $H_4SiW_{12}O_{40}$, and $H_3PMo_{12}O_{40}$ hydrate from Aldrich, Merck and. Carbon, KSF and K10 montmorillonite clay were obtained from Fluka. γ-Alumina and titania were obtained from Aldrich and Degussa respectively. The tungsten or molybdenum content in the catalysts was measured by inductively coupled plasma (ICP) atomic emission spectroscopy on a Spectro Ciros CCd spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance 200 MHz NMR spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard.

PREPARATION OF THE CATALYSTS

The catalysts were prepared using solutions of tungstophosphoric acid (PW), molybdophosphoric acid (PMo), or tungstosilicic acid (SiW). The solutions were used to impregnate supports with different characteristics. The solids employed as supports were activated carbon, γ-Al_2O_3, TiO_2, KSF and K 10 montmorillonites.

Titania-supported PW (PW/TiO_2) catalysts were prepared by impregnating titania (5.0 g) with an aqueous solution of PW (with concentrations depending upon the loadings, 20, 40 and 60 wt% PW on titania). The mixture was stirred overnight at rt, followed by drying using a rotary evaporator. For preparation of the PW/K 10, K 10 montmorillonite was dried in an oven at 120 °C for 2 h prior to its use as support. After drying, 5.0 g of K 10 was taken. To prepare a catalyst with 40% loading of PW, 2.0 g of PW was dissolved in 4 cm^3 of dry MeOH. This solution was added dropwise to predried K 10 with constant stirring with a glass rod. Initially with addition of PW solution, the clay was in the powdery form, but on further addition of PW solution, the clay turned to a paste form. The paste on further stirring for 10 min resulted in a free flowing powder. A similar procedure was followed for the synthesis of PW/KSF. A catalyst based on PW supported on γ-Al_2O_3 was also prepared. The solution of PW was prepared by dissolving 2.0 g of PW in 25 cm^3 of water and 25 cm^3 of MeOH. Then 5.0 g of γ-Al_2O_3 was dropped into the above solution under vigorous stirring to be impregnated for 24 h. For preparation of PW/C, carbon was first subjected to an acid and base treatment to remove impurities. The catalyst was prepared by the pore filling impregnation technique with a PW solution. After the impregnation, all catalysts were dried at rt for 24 h, and calcined at 200 °C for 3 h.

TYPICAL PROCEDURE FOR HANTZSCH THREE COMPONENT CONDENSATION

A mixture of aldehyde (1 mmol), β-dicarbonyl compound (2 mmol, and 1 mmol for entries 11, 12, Table 2), amine (1 mmol) and appropriate amount of the catalyst (Table 1), was stirred at ambient temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solid product was crushed, diluted with acetonitrile (2×5 cm^3) and filtered. Filtrate was concentrated in *vaccuo* to afford the crude product. A pure product was obtained as a yellow solid by further recrystallation in

ethanol. At the end of the reaction, the reaction mixture was treated with MeCN and filtered to recover the catalyst. The wet catalyst was washed with ether and recycled to check the reusability of the catalyst.

TYPICAL PROCEDURE FOR HANTZSCH FOUR COMPONENT CONDENSATION

A mixture of aldehyde (1 mmol), EtOAc (1 mmol), dimedone (1 mmol) and ammonium acetate (1 mmol) was stirred at 80 ºC in the presence of appropriate amount of the catalyst (Table 1) until all reactants were consumed (monitored by TLC). Purification of products and recyclization of the catalyst are similar to above procedure.

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