

## Tungstophosphoric Acid Supported on Silica Gel ( $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$ ) as an Eco-Friendly, Reusable and Heterogeneous Catalyst for the Synthesis of Pyrroles in Solution or under Solvent-Free Microwave Irradiation

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Heteropoly acid supported on silica gel ( $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$ ) is easily used as a heterogenous, reusable and efficient catalyst for the synthesis of *N*-substituted, 2- and 3-unsubstituted pyrroles in solution or under solvent-free microwave irradiation. The catalyst can be easily recovered and reused for several times without loss of activity.

**Keywords:**  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$ , Pyrrole, Clauson-Kass reaction, Microwave, Solvent-free, Amine

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### INTRODUCTION

The pyrrole ring system is a useful structural element in medicinal chemistry [1] which has found wide application in drug development and is used in antibacterial, antiviral, anti-inflammatory, antitumoral treatments, and as an antioxidant [2]. They are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry [3] and are widely used in materials science [4]. It is, therefore, not surprising that many synthetic methods have been developed for the preparation of these compounds [5].

The Clauson-Kass pyrrole synthesis involves the condensation reaction of the amine with 2,5-dimethoxytetrahydrofuran for the synthesis of the *N*-substituted, 2- and 3-unsubstituted pyrroles, where the 2- and 3-positions can be reacted for further functionalisation. To date, a number of catalysts such as glacial acetic acid [6], TfOH [7],  $\text{P}_2\text{O}_5$  [8], MW irradiation [9a], montmorillonite K-10/MW [9b],  $\text{FeCl}_3$  [9c],  $\text{Sc}(\text{OTf})_2$  [9d] and 4-chloropyridine hydrochloride [10] have been used to promote these condensations. No reaction is

observed in the absence of the catalyst [9c].

In the preparation of pyrroles, factors such as harsh reaction conditions, long reaction times [9], high reaction temperature [11,9c], strictly anhydrous condition [8], using expensive reagents [7,9c], impose severe limitations on the use of existing methods. In addition, some of the reagents or catalysts are not eco-friendly and are not recoverable or reusable materials. Although scandium triflates [9c] applied for this purpose are attractive, they are, however, rather expensive; thus, their use especially for the large-scale synthetic operations, may not be recommended from the economical point of view. Hence, cheaper and commercially available catalysts that promote catalytic activity, low toxicity, high stability towards humidity, and air tolerance are worth exploration and developing new methods which use less hazardous solvents or none at all is in order. Therefore, the search continues for better catalysts for the synthesis of pyrroles in terms of operational simplicity, economic viability, and greater selectivity.

The development of methods using heteropolyacids (HPAs) as catalysts for fine organic synthetic processes related to fine chemicals, such as flavors, pharmaceuticals and food

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industries [12] has been an area of research in the last decades.

Heteropoly acids are more active catalysts than the conventional inorganic and organic acids for various reactions in solutions [13]. They are used as industrial catalysts for several liquid-phase reactions [14-17]. Among heteropoly acids, polytungstic acids are the most widely used catalysts owing to their high acid strengths, thermal stability, and low reducibility. Catalysts based on heteropoly acids such as Bronsted acids have many advantages over liquid acid catalysts. They are non-corrosive and environmentally benign, presenting fewer disposal problems. Solid heteropoly acids have attracted special attention in organic synthesis owing to easy work-up procedures, easy filtration, and minimization of cost and waste generation due to the reusability and recyclability of the catalysts [18]. Supported heteropoly acid on silica gel has been used as an effective catalyst for Diels Alder [19a] and Fries rearrangement [19b], Friedel Crafts reactions [19c,d], oxathioacetalization of carbonyl compounds [20a], synthesis of  $\beta$ -acetamido ketones [20b], Isomerisation of  $\alpha$ -pinene oxide [20c], and photocatalytic oxidation of benzylic alcohols to carbonyl compounds [20d].

In the last few years, we have concentrated on the exploration of new catalytic activities of  $H_3PW_{12}O_{40}$  and its salts [12d,12e,20a,20e], for basic chemical transformations. In this article, we report that  $H_3PW_{12}O_{40}$  supported on silica gel ( $H_3PW_{12}O_{40}/SiO_2$ ) could be used as a highly efficient catalyst for the condensation of amines with 2,5-dimethoxytetrahydrofuran to produce *N*-substituted, 2- and 3-unsubstituted pyrroles in solution or under solvent-free microwave irradiation (Scheme 1).

## EXPERIMENTAL

### General Procedure for the Synthesis of Pyrroles

Method A: To a solution of amine (1 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol) in petroleum ether 40-60 was added HPA/SiO<sub>2</sub> 10% (2.5 mol%) and stirred to

consume the starting material as specified in Table 2. After the completion of the reaction, diethyl ether (10 ml) was added to the reaction mixture and the catalyst was recovered by a simple filtration. Petroleum ether/diethyl ether was removed by a simple distillation. The sole corresponding pyrroles were obtained after the recrystallization in ethanol-water and consequently simple filtration.

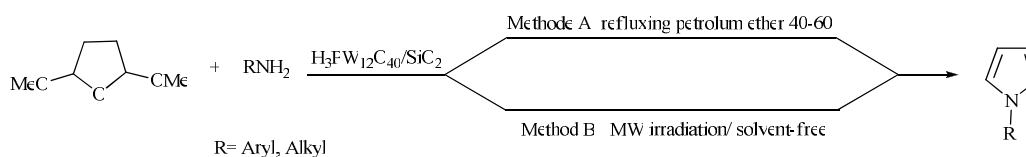
Method B: Amine (1 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol), and HPA/SiO<sub>2</sub> 10% (2.5 mol%) were mixed carefully, put in the MW vessel and irradiated in the microwave oven as specified in Table 2. After the completion of the reaction, diethyl ether (10 ml) was added to the reaction mixture to dissolve the product and the catalyst was recovered by a simple filtration. Diethyl ether was removed by a simple distillation. The sole corresponding pyrroles were obtained after recrystallization in ethanol-water and consequently simple filtration.

### Selected Analytical and Spectral Data for New Compounds

**1-(3-Pyrrole-1-phenyl)-ethanone (Table 2, entry 9).** M.p.: 55-56 °C; FT-IR:  $\nu_{\max}(\text{neat}) = 3064, 1681, 1587, 1497, 1444, 1340, 1249, 1075, 723, 687 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 2.64 \text{ (s, 3H)}, 6.29 \text{ (s, 2H)}, 7.46 \text{ (s, 2H)}, 7.59 \text{ (dd, } J = 8.0, 7.6 \text{ Hz, 1H)}, 7.80 \text{ (d, } J = 7.6 \text{ Hz, 1H)}, 7.83 \text{ (d, } J = 8 \text{ Hz, 1H)}, 8.03 \text{ (s, 1H) ppm}$ ; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 27.3, 110.9, 111.3, 111.6, 119.1, 119.6, 124.2, 124.9, 125.3, 129.7, 130.5, 138.6, 140.6, 198.0 \text{ ppm}$ .

**1-(3-((1H-pyrrol-1-yl)methyl)benzyl)-1H-pyrrole (Table 2, entry 10).** M.p.: 92-93 °C; FT-IR:  $\nu_{\max}(\text{neat}) = 3000, 2930, 1607, 1520, 1443, 1407, 1325, 1301, 974, 751 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 4.72 \text{ (s, 4H)}, 4.99 \text{ (s, 4H)}, 5.89 \text{ (s, 4H)}, 6.58 \text{ (s, 1H)}, 6.74 \text{ (d, } J = 7.5 \text{ Hz, 2H)}, 7.24 \text{ (t, } J = 7.5 \text{ Hz, 1H) ppm}$ ; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 47.1, 105.9, 123.5, 124.8, 128.3, 129.7, 139.5 \text{ ppm}$ .

**Bis(4-(1H-pyrrole-1-yl)phenyl)methan (Table 2, entry 11).** M.p.: 94-95 °C; FT-IR:  $\nu_{\max}(\text{neat}) = 2919, 1516, 1402,$



Scheme 1

Tungstophosphoric Acid Supported on Silica Gel (H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>/SiO<sub>2</sub>)

1320, 1105, 1036, 998, 768, 754 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 3.96 (s, 2H), 6.22 (s, 4H), 7.30 (d, *J* = 7.6 Hz, 8H), 7.47 (d, *J* = 7.6 Hz, 4H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 40.2, 110.7, 119.4, 119.9, 130.3, 138.6, 138.8 ppm.

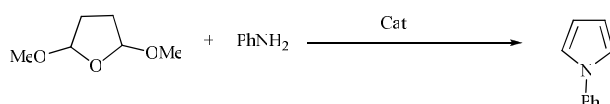
## RESULT AND DISCUSSION

For the optimization of the reaction conditions, the reaction of aniline (1 mmol) with 2,5-dimethoxytetrahydrofuran (1.2 mmol) in the presence of a catalytic amount of unsupported and supported H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> on silica gel was studied. The best reaction condition was observed when the reaction occurred in the presence of 2.5 mol% of H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>/SiO<sub>2</sub> under refluxing petroleum ether 40-60. Under this condition, the reaction proceeded well and completed after 1.5 h to produce the desired N-phenyl pyrrole in 93% isolated yield. We have also studied a similar reaction in the presence of silica gel. The reaction did not proceed well and the product was produced in less than 10% after 24 h (Table 1). These

findings show the strong synergistic effect of silica gel upon the catalytic activity of H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> in the reaction of aniline with 2,5-dimethoxytetrahydrofuran (Table 1). In addition, prompted by the current challenges for developing solvent-free and environmentally benign protocols, we studied the reaction of aniline with 2,5-dimethoxytetrahydrofuran under solvent-free microwave irradiation conditions in the presence of this catalyst (Table 1, entries 12-15). We found that solvent-free microwave irradiation condition was a more suitable and efficient one. Furthermore, the catalyst was easily separated from the reaction mixture by a simple filtration after the addition of diethyl ether to the reaction mixture. The catalyst can be reactivated (150 °C) and reused for at least four runs (Table 2). The pyrrole products were crystallized upon concentration and addition of ice-water to the filtrated solution in excellent yield. The results are displayed in Table 1.

Encouraged by these findings, we started the reaction of a variety of amines with 2,5-dimethoxytetrahydrofuran to probe the scope and reactivity of the new catalyst the results of which are summarized in Table 3. As can be seen from Table

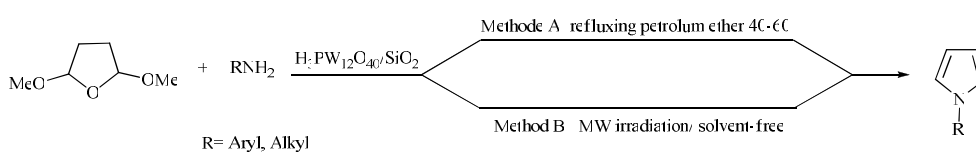
**Table 1.** The Optimization of Reaction Conditions



Entry	Cat (w%)	Mol%	Solvent	Condition	Time (h)	Yield (%)
1	SiO <sub>2</sub>	2.5	Petroleum ether 40-60	reflux	24	<10
2	HPA	2.5	Petroleum ether 40-60	reflux	4	85
3	HPA/SiO <sub>2</sub> (10)	2.5	Petroleum ether 40-60	reflux	1.5	92
4	HPA/SiO <sub>2</sub> (10)	1.0	Petroleum ether 40-60	reflux	8	93
5	HPA/SiO <sub>2</sub> (10)	2.0	Petroleum ether 40-60	reflux	3	92
6	HPA/SiO <sub>2</sub> (15)	2.5	Petroleum ether 40-60	reflux	1.5	90
7	HPA/SiO <sub>2</sub> (5)	2.5	Petroleum ether 40-60	reflux	4.30	91
8	HPA/SiO <sub>2</sub> (10)	2.5	Petroleum ether 40-60	rt	12	94
9	HPA/SiO <sub>2</sub> (10)	2.5	Toluene	60	2.30	91
10	HPA/SiO <sub>2</sub> (10)	2.5	<i>n</i> -Hexane	60	2.45	90
11	HPA/SiO <sub>2</sub> (10)	2.5	Acetonitrile	60	7	92
12	HPA/SiO <sub>2</sub> (10)	2.5	-	MW (power 5)	6 min	91
13	HPA/SiO <sub>2</sub> (10)	2.5	-	MW (power 8)	3 min	93
14	HPA/SiO <sub>2</sub> (10)	2.5	-	MW (power 10)	3 min	92
15	SiO <sub>2</sub>	0.3 g	-	MW (power 8)	10 min	5

**Table 2.** Reusability of  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  (10% W/W) in the Synthesis of 1-Phenyl-1H-pyrrole

Entry		1 <sup>th</sup>	2 <sup>th</sup>	3 <sup>th</sup>	4 <sup>th</sup>
Method A: under refluxing pet-ether 40-60	Yield (%) / Time (h)	1.5/92	2/93	2/92	2/90
Method B: under solvent-free MW irradiation		3/93	5/93	5/91	5/90

**Table 3.** Formation of Pyrroles from Various Amines<sup>a</sup>

Entry	Substrate	Product <sup>b</sup>	Time/Yield		m.p. (reported)	Ref.
			Method A (h)/(%)	Method B <sup>c</sup> (min)/(%)		
1			1.5/92	3/93	59-60	[9a]
2			6/91	6/93	79-80	[9a]
3			6/90	6/90	50	[9a]
4			3/90	6/94	111-112	[9a]
5			4/87	6/96	56-57	[9c]
6			4/90	6/90	82-83	[9a]

Table 3. Continued

7			24/60	30/91	180-182	[9a]
8			24/70	20/90	67-68	
9			10/91	25/93	55-56	
10 <sup>d</sup>			9/93	9/95	137-138	
11 <sup>d</sup>			10/90	20/90	166-167	

<sup>a</sup>The reaction conditions: amine (1 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol),  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  (2.5 mol%). <sup>b</sup>Yields refer to isolated pure products which were characterized by comparison of their mp, IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra with those of authentic samples. <sup>c</sup>The Microwave oven Kenwood (1300 W, 2450 MHz) was used for running the described reactions. <sup>d</sup>The reaction conditions: diamine (1 mmol), 2,5-dimethoxytetrahydrofuran (2.5 mmol),  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  (2.5 mol%).

2, reactions examined with most of the amines containing strong electron-deficient (*p*-NO<sub>2</sub>, and *m*-NO<sub>2</sub>, *p*-CN, *m*-COCH<sub>3</sub>) and strong electron-donating (*p*-MeO) aniline produced good to excellent yields of the corresponding pyrroles. It is of particular note that, in the case of strong electron-deficient amine a longer reaction time was needed.

Bispyrroles are interesting compounds which they can be employed, for example, as the monomers for the preparation of macrocyclic or polymeric compounds carrying pyrrole structure. In this study, we also investigated the applicability of the method for the preparation of bispyrroles *via* the reaction of diamines, and 2,5-dimethoxytetrahydrofuran in the presence of  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  (0.3 g, 1 mol%). The reactions progressed well both in solution and under solvent-free

microwave irradiation and the desired bispyrroles were produced in high yields (Table 3, entries 10, 11).

In conclusion, we have demonstrated that  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  is a highly effective heterogeneous catalyst for condensation of various primary amines with 2,5-dimethoxytetrahydrofuran. The main advantages of the protocol are that it proceeded smoothly and selectively in the presence of moisture under solvent-free conditions, and produced pyrrole and bispyrrole in high to excellent yields in solvent or solvent-free MW irradiation.  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  is stable, reusable and an environmental friendly catalyst that affords easy handling and simple work-up. Furthermore, this method is a useful addition to the present methodologies used for the synthesis of pyrrole, especially for the synthesis of less available bispyrrole.

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