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$Cs_xH_{3-x}PW_{12}O_{40}$ heteropoly salts catalyzed quinoline synthesis *via* Friedländer reaction

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Abstract

Various type of cesium partially substituted phosphotungstate, $Cs_xH_{3-x}PW_{12}O_{40}$ (x = 1.0, 2.0 and 2.5), were synthesized and their catalytic activities were investigated in the synthesis of quinoline. It was shown that catalytic activities of these catalysts correlated to surface acidity and total number of acidic sites. Finally, a series of quinoline derivatives were synthesized with $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ via the Friedländer reaction in high to excellent yields and the plausible mechanism was proposed. Simple experiment, catalyst reusability, short reaction time and preclusion of toxic solvent are the advantages of this method.

Keywords: Quinoline; Friedländer reaction; Cesium Keggin salts; Acidity

Quinoline is a well-known structural unit in several natural compounds (cincona alkaloids) and synthetic analogues with interesting biological activities [1]. The biological activity of quinoline derivatives has been found to possess antiasthmatic, antibacterial and antihypertensive properties [2]. The Friedländer reaction is a well-known, simple, and most straightforward protocol for preparing quinolines and related bicyclic compounds. It is a condensation reaction followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone and an aldehyde or ketone with an α-methylene functionality under acidic or basic conditions [3]. Several solid acid catalysts have been used in the Friedländer reaction including $Ag_3PW_{12}O_{40}$ [4], sulfamic acid [5], $HClO_4$–SiO_2 [6], amberlyst-15 [7], dodecylphosphonic acid [8] and *o*-benzenedisulfonimide [9]. Although some of these methods have convenient protocols with good to high yields, the majority of these methods suffer from drawbacks such as the presence of hazardous and toxic solvents [4,6,7], long reaction times or unsatisfactory yields for some substrates [5,7–9], and use of expensive or non-commercially available catalysts [9]. Since, quinoline derivatives are useful in drugs and pharmaceuticals, the development of simple, convenient and high yielding protocols is much needed.

Rapid development of science and technology requires the development of new catalysts and methodologies with low waste and reusable reaction media for minimized cost and energy. In order to achieve this goal, use of Keggin type heteropoly compounds (HPCs) as catalyst is preferred technique owing to their versatility and unique properties which has been demonstrated both by successful industrial applications, and by interesting results in laboratory scale work.

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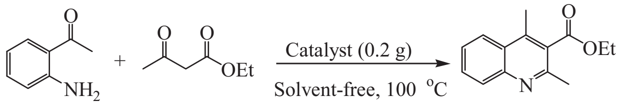


Scheme 1. Model reaction.

The structure and composition of HPCs play an important role in catalysis and their catalytic properties can be controlled in a systematic way by partially exchanging protons of the parent HPCs with large cations, such as Cs^+, K^+, Rb^+, or NH_4^+ [10]. Partial substitution of Cs^+ for protons in $Cs_xH_{3-x}PW_{12}O_{40}$ catalysts improved surface area and thermal stability compared to parent acids. Also, the surface acidity, and pore width can be controlled by the Cs content [11]. These compounds are efficient solid acid catalysts for a variety of organic reactions, such as alkylation [10], esterification [12], condensation [13], and biodiesel fuel preparation [14]. According to our previous investigations [12,13], herein we want to report the applicability of $Cs_xH_{3-x}PW_{12}O_{40}$ in the synthesis of quinolines. The reaction of 2-aminoacetophenone (1.0 mmol) and ethylacetoacetate (1.2 mmol) under solvent-free conditions at 100 °C was selected as the model reaction in all cases (Scheme 1).

Initially, this conversion has been carried out in the presence of 0.2 g of $H_3PW_{12}O_{40}$ (PW_{12}) and its partial substituted acidic Cs salt catalysts containing $Cs_1H_2PW_{12}O_{40}$ (Cs_1PW), $Cs_2H_1PW_{12}O_{40}$ (Cs_2PW), and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ ($Cs_{2.5}PW$). Potentiometric titration with *n*-butylamine has been used to estimate the total number of acid sites and the acidic strength of these catalysts. The *n*-butylamine is considered a strong base, so its adsorption could be expected on sites of different acid strength. Taking into account that the initial electrode potential (E_i) indicates the highest strength of the acid sites and the obtained plateau value (meq amine/g catalyst) indicates the total number of acid sites that are present in the titrated solid [15]. The strength of the acid sites can be classified according to the following scale: $E\text{i} > 100$ mV (very strong sites); $0 < E\text{i} < 100$ mV (strong sites); $-100 < E\text{i} < 0$ mV (weak sites); and $E\text{i} < -100$ mV (very weak sites) [15]. All the catalysts exhibit very strong acidic sites as they showed high *E*i values, which are found to vary in the range of 200–700 mV. Fig. 1a shows yield and *E*i amount as a function of Cs content. The maximum acid strength of the sites (bulk Brønsted acidity) changed in following order: $PW_{12} > Cs_1PW > Cs_2PW > Cs_{2.5}PW$ [11]. The *E*i values and yields are in the same order except for $Cs_{2.5}PW$. In contrast, both catalytic activity and total number of surface acidic sites decreased slightly from $x = 0$ to $x = 2$, although these amounts increased when the Cs content changed from $x = 2$ to $x = 2.5$ (Fig. 1b). Consequently, the dependence of surface acidity and catalytic activity of $Cs_xH_{3-x}PW_{12}O_{40}$ to Cs content is remarkable. The surface area and acidity of Cs salt of heteropoly acid (HPA) were influenced largely by the number of substituted Cs^+. For $Cs_{2.5}PW$ surface area is large and catalytic activity of $Cs_{2.5}PW$ was ascribed to its high surface acidity [11].

In order to extent the scope of this system, various activated α-methylene compounds were used as substrates to undergo Friedländer reaction using $Cs_{2.5}PW$ as the best catalyst. The results are summarized in Table 1. β-Ketoesters and acyclic β-diketones worked successfully owing to higher reactivity and gave excellent yield of the products (Table 1, entries 1, 2, 4, 5). Dimedone, 4-methylacetophenone and acetophenone provided the corresponding enamine as a by-product in low yield, while cyclohexanone gave only enamine as a final product (Table 1, entries 3, 6, 8, 9).

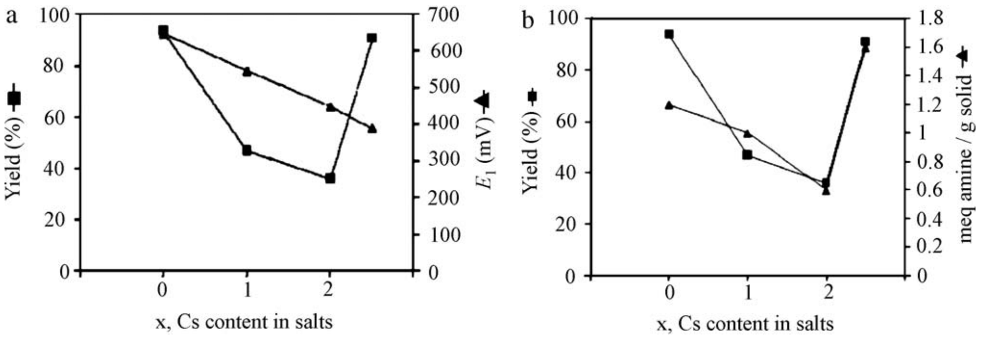
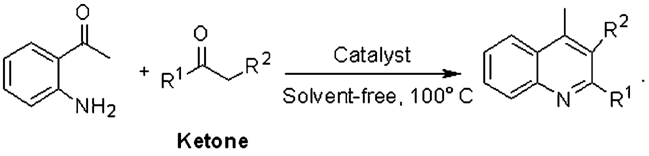


Fig. 1. Yield of the product in the model reaction after 20 min: (a) acidity and (b) total number of acidic sites of the catalysts as a function of cesium content in $Cs_xH_{3-x}PW_{12}O_{40}$.

Table 1

Synthesis of quinoline derivatives in the presence of $Cs_{2.5}PW$.



Entry	Ketone	Time (min)	Yield (%)[a,b]	Conversion (%)
1	Ethylacetoacetate	15	91	91
2	Methylacetoacetate	25	98	98
3	Dimedone	15	88	97
4	Benzoylacetone	5	83	83
5	Acetylacetone	20	96	96
6	Cyclohexanone	30	82[c]	82
7	4-Nitro-acetophenone	10	93	93
8	4-Methylacetophenone	15	85	94
9	Acetophenone	15	61	82

[a] Isolated yield.

[b] Identified by spectroscopic (IR, ^1H NMR) analyses.

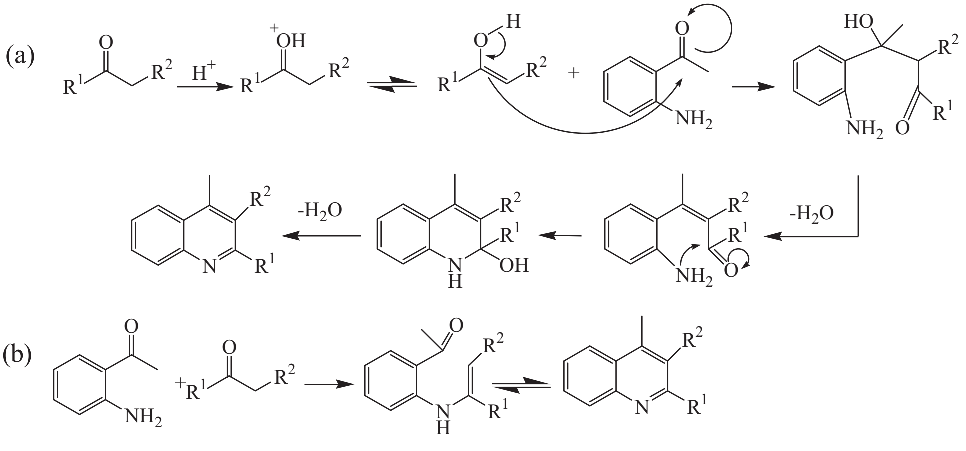
[c] Yield of corresponding enamine.

Acetophenone with an electron withdrawing substitute in para position improved the yield in the reaction process (Table 1, entry 7).

There are two possible reaction mechanisms that are shown in Scheme 2 [16,17]. The results of the reaction of cyclohexanone with 2-amino acetophenone (Table 1, entry 6) confirmed that mechanism b is the possible one, which enamine was formed as an intermediate. Proton conductivity of HPAs as acid catalysts is completely essential to activate carbonyl compound. In the Friedländer synthesis, a crossed-aldol reaction takes place initially, creating an amino ketone. This intermediate subsequently condenses with itself, and produced the ring with concomitant formation of the carbon–nitrogen double bond.

The results after reusing of $Cs_{2.5}PW$ for three times in model reaction indicate that $Cs_{2.5}PW$ is a reusable catalyst and yield of product was 76% after fourth run. Conversion was approximately constant, but selectivity of the reaction has been slightly decreased (81% after fourth run), it is because of formation of side product.

$Cs_xH_{3-x}PW_{12}O_{40}$ ($x = 1.0$, 2.0 and 2.5) compounds were active catalysts for the reaction of 2-aminoacetophenone and ethylacetoacetate under solvent-free conditions. Among these acidic Cs salts, $Cs_{2.5}PW$ was most active. This is due to the largest amount of acid sites on the surface (surface acidity). Thus, various activated α-methylene



Scheme 2. Proposed mechanism.

compounds were used as substrate to undergo Friedländer reaction using $Cs_{2.5}PW$ as catalyst. The catalyst could be easily recovered and reused without a considerable change in its catalytic activity. Also, the plausible mechanism was proposed according to enamine which was formed as an intermediate.

1. Experimental

For the potentiometric titration, 0.05 g of solid was preheated and suspended in acetonitrile (90 ml) and stirred for 3 h. The suspension was titrated with a 0.05 mol/L solution of *n*-butylamine in acetonitrile. The potential variation was measured with a Hanna 302 pH meter using a double junction electrode.

1.1. Preparation of $Cs_xH_{3-x}PW_{12}O_{40}$

The acidic salts of $Cs_xH_{3-x}PW_{12}O_{40}$ were prepared by the literature method [11]. The required amount of aqueous cesium carbonate has been added to aqueous solution of PW_{12} with stirring. An appropriate amount of the aqueous solution of Cs_2CO_3 (0.10 mol/L) was added drop wise to the aqueous solution of PW_{12} (0.08 mol/L) at room temperature with vigorous stirring. The Cs content was adjusted by the amount of Cs_2CO_3 solution added. The resulting white colloidal solutions of Cs salts were left overnight in the oven at 40 °C to slowly evaporate to dryness. Cesium content in $Cs_xH_{3-x}PW_{12}O_{40}$ catalysts was confirmed by inductively coupled plasma (ICP) atomic emission spectroscopy on a Spectro Ciros CCd spectrometer. The primary Keggin structures of these catalysts were identified by comparing their FTIR absorption bands to those of bulk PW_{12} as reported elsewhere [18].

1.2. General procedure for Friedländer reaction

A mixture of 2-amino acetophenone (1.0 mmol), α-methylene carbonyl compound (1.2 mmol) and catalyst (0.2 g) were added to a pyrex tube fitted with a ground glass joint. These compounds were ground together using a glass rod at 100 °C. After reaction completion, as indicated by TLC, the reaction mixture was cooled and diluted with CH_3CN (5 mL) and filtered. The catalyst was recovered from residue. The filtrate was concentrated and product was purified by column chromatography on silica gel using ethylacetate/hexane as eluent. Recovered catalyst was washed with CH_3CN (3 × 10 mL) and reused.

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