



## Ecofriendly ketalization of isatin using heteropolycompounds as catalysts

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### ARTICLE INFO

#### Article history:

Received 5 October 2007

Received in revised form 11 July 2008

Accepted 16 August 2008

Available online 26 August 2008

#### Keywords:

Keggin heteropolycompounds  
Heteropolyphosphotungstic acid  
Isatin  
Ketalization

### ABSTRACT

The dioxolane ketals of isatin and 5-chloroisatin were prepared using an efficient and cleaner procedure than the usual synthetic routes. Keggin heteropolyacids, namely, heteropolyphosphotungstic acid (HPW), HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW, have proven to be useful catalysts, allowing to the fast, selective and solvent-less preparation of ketals, with high yields and 100% selectivity.

The homogeneous HPW catalyst may be successfully heterogenized by partial exchange of H<sup>+</sup> for Cs<sup>+</sup> but some evidences were found of significant homogeneous contributions of leached HPW when the silica supported catalysts (HPW/SiO<sub>2</sub>) was used in the ketalization reaction. The Cs<sub>2.2</sub>HPW (Cs<sub>2.2</sub>H<sub>0.8</sub>PW<sub>12</sub>O<sub>40</sub>) catalysts may be repeatedly used but a progressive activity loss was assigned to residual organic materials that could not be removed after several dichloromethane washings.

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### 1. Introduction

Isatin, 1*H*-indole-2,3-dione **1**, and its derivatives are important raw materials for the syntheses of several pharmacologically active molecules such indol and quinolinic heterocyclic compounds [1]. For instance, isatin and 5-haloisatin ketals, such as the dioxolane ketal of 5-chloroisatin **4**, have significant anticonvulsant and anxiolytic activities [2]. In these syntheses, the ketalization with ethyleneglycol is usually required as a previous step to protect of the carbonyl group of the isatin [3].

The ketalization of carbonyl compounds is thermodynamically limited; the reactions are slightly endothermic and show negative entropy variation. In order to overcome these limitations, the chemical equilibrium may be shifted toward the production of ketals, using higher reaction temperatures, excess of alcohol or removing water from the reaction media [4]. This reaction is usually activated by the protonation of the oxygen on the carbonyl group in such a way that acid catalysts should be useful to speed up the isatin ketalization.

Both homogeneous and heterogeneous acid catalysts have been successfully used in preparation of isatin ketals, but the use of heterogeneous catalysts is preferred as an ecofriendly process may be achieved, reducing or even avoiding the use of a large amount of solvents and further separations steps [5].

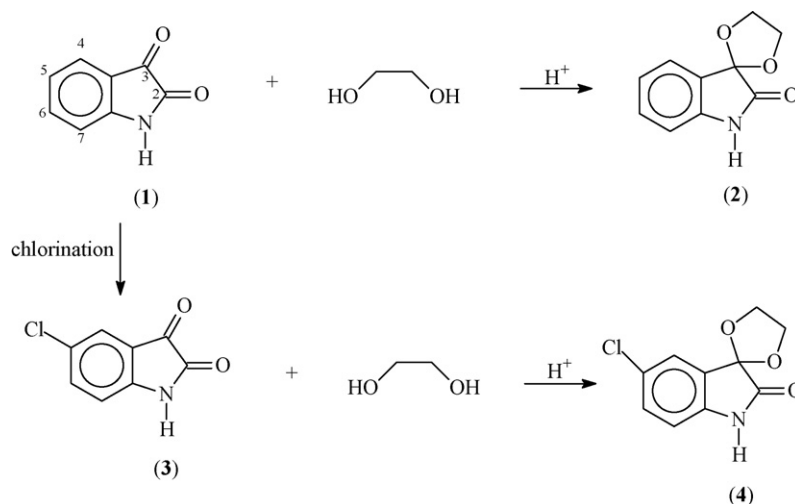
Organic and inorganic acids such as *p*-TsOH, H<sub>2</sub>SO<sub>4</sub> and Keggin heteropolyacids have been used to prepare cyclohexanone ketals [6] and, more recently, isatin ketals have been successfully prepared using acid activated clays and microwave radiation [5].

Heteropolyacids and their salts have been extensively studied as ecofriendly catalysts for several organic reactions, either in redox or acid–base mechanisms [7]. Those containing the Keggin unit, [XM<sub>12</sub>O<sub>40</sub>]<sup>x−8</sup>, where *x* is oxidation state of X, are the most studied for catalysis applications [8]. The heteropolyphosphotungstic acid, H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (HPW), is considered to be the strongest acid of the series of Keggin heteropolyacids [9].

HPW is soluble in several solvents and, in order to be used as heterogeneous catalysts in organic reactions, it is generally supported on a porous solid, such as silica, increasing the catalytic surface area and the accessibility to the acid sites [10]. Alternatively, HPW may be heterogenized by partial exchange of H<sup>+</sup> for cations, such as K<sup>+</sup>, Cs<sup>+</sup> and NH<sub>4</sub><sup>+</sup>. The resulting salts are porous and insoluble in polar solvents. Cs<sub>2.5</sub>H<sub>0.5</sub>PW<sub>12</sub>O<sub>40</sub> (100–200 m<sup>2</sup> g<sup>−1</sup>) is one of the most studied and has been proven to be active for aromatic alkylation, isomerization and olefin hydration reactions [11].

In order to develop an ecofriendly methodology to prepare isatin ketals, the soluble heteropolyphosphotungstic acid (H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>) has been impregnated on a silica support and partially neutralized with Cs<sup>+</sup> ions. The parent H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> and the resulting H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>/SiO<sub>2</sub> and Cs<sub>2.2</sub>H<sub>0.8</sub>PW<sub>12</sub>O<sub>40</sub> catalysts were used in the ketalization of isatin **1** and of 5-chloroisatin **4**, as shown in Scheme 1.

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**Scheme 1.** Ketalization of isatin **1** and 5-chloroisatin **4**.

## 2. Experimental

### 2.1. Chemicals and catalysts

Reactants and solvents (provided either by Merck or Aldrich) were used without any further purification. High purity HPW, provided by Merck, was purified by ethyl ether extraction from water solution. The etherate was evaporated at room temperature and heated at 110 °C for 2 h and further on at 150 °C for 3 h [8]. Silica (Aerosil 380) was provided by Degussa.

The supported catalyst (40% HPW/SiO<sub>2</sub>) was prepared by impregnation. After thoroughly mixing the aqueous slurry for 8 h and evaporating at 110 °C to dryness, the supported catalyst was further heated at 150 °C for 3 h [8]. The HPW loading in the final catalyst was determined by FRX (X-ray fluorescence). The cesium salt of HPW was prepared by drop wise addition of 50 mL of an aqueous solution containing 0.407 g of cesium carbonate to 70 mL of an aqueous solution containing 2.957 g of HPW, under stirring, at room temperature. The white precipitate was centrifuged (4000 rpm, for 30 min), washed with deionized water, dried in an evaporator at 45 °C and finally calcined at 300 °C, for 3 h [10]. The composition of this material, as determined by FRX, was Cs<sub>2.2</sub>H<sub>0.8</sub>PW<sub>12</sub>O<sub>40</sub> and will be referred herein as Cs<sub>2.2</sub>HPW.

XRD (Shimadzu XRX-6000 diffractometer); FTIR (PerkinElmer Spectrum BX), nitrogen adsorption (Micromeritics ASAP 2020) and thermogravimetry (Shimadzu TG-50) techniques were used in order to characterize the catalysts. The characterization procedures were described elsewhere [10].

The acid properties of the catalysts were investigated using three different methods, namely, TGA after adsorption of cyclohexylamine; potentiometric titration with 0.05N *n*-butylamine in acetonitrile and NH<sub>3</sub> TPD.

For the weight loss analysis, the catalyst sample was initially heated under dry nitrogen atmosphere at 400 °C for 2 h; cooled down to 95 °C and saturated with cyclohexylamine at this temperature. The system was purged at 95 °C for more 2 h in flowing dry nitrogen. The sample was then transferred to the TGA balance and analyzed at a heating rate of 10 °C/min in a dry N<sub>2</sub> flow of 50 mL/min. A blank run was undertaken in order to follow the typical weight loss profile of the catalyst without adsorbed cyclohexylamine.

The potentiometric titrations were carried out using 1 g samples of the catalysts in 50 mL of acetonitrile, under stirring, at 25 °C and

600 rpm. The initial potential was measured after electrode signal stabilization. Aliquots (0.5 mL) of *n*-butylamine 0.05N in acetonitrile were added and the potential recorded after stabilization of readings [12,13].

The NH<sub>3</sub>-TPD profiles were collected in a Micromeritics Chemisorb 2720. After pretreatment in helium (300 °C, 25 mL min<sup>-1</sup>, 1 h), the TPD cell containing the sample (0.1 g) was cooled down to 25 °C; ammonia was fed (10% NH<sub>3</sub> in helium) for 30 min and then purged with helium for 1 h. The temperature was again increased at 10 °C/min up to 150 °C in a helium flow and held for 30 min to remove weakly adsorbed ammonia. The desorption profiles were collected in the temperature of 25–700 °C, at a rate of 10 °C/min, in a 30 mL/min helium flow [14].

HPW leaching from the silica support in ethyleneglycol was determined, at 23 °C, using an UV-vis spectrophotometer (Shimadzu UV-1650 PC).

### 2.2. Reactions studies

**Isatin chlorination:** 5-chloroisatin **4** was prepared by reacting isatin **1** (0.5 g), sodium dichloroisocyanide (0.6 g, 2.73 mmol) and sulfuric acid (6 mL), under stirring, in an ice bath, for 30 min [15,16]. The crystals were then separated under vacuum filtration and further washed with distilled water. The preparation yield of 97% in 5-chloroisatin **4** was determined by GC-MS.

5-Chloroisatin **4**, (5-Chloro-1H-indole-2,3-dione): (C<sub>8</sub>H<sub>4</sub>NClO<sub>2</sub>). MS (70 eV): 183 (14), 181 (41), 153 (100), 125 (30), 110 (3), 98 (13), 90 (14), 75 (8), 63 (29). IR (cm<sup>-1</sup>): 3452, 3182, 3081, 3002, 2920, 1749, 1707, 1618, 1453, 1270, 1123, 848, 745, 464. <sup>13</sup>NMR (75 MHz, CDCl<sub>3</sub>): 114.0; 118.5; 124.6; 128.3; 137.7; 149.4; 159.1; 183.7.

**Isatin **1** and 5-chloroisatin **4** ketalization:** the experiments were performed at different reaction conditions, using HPW, HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW catalysts. The reactions were carried out at the temperature range of 23–100 °C, using a round bottom flask (50 mL) equipped with a reflux condenser, magnetic stirrer (300–1000 rpm) and thermometer. Typically, the catalyst was added (*t*=0) to a mixture containing 0.68 mmol of either isatin (100 mg) or 5-chloroisatin (123 mg) and ethyleneglycol (33 mL), at the reaction temperature. Duplicate reaction runs were carried out in order to obtain reproducible results. Samples (~0.2 mL) were periodically collected and analyzed off-line in a GC-MS (Shimadzu-QP 5050), using a DB-5, 30 m capillary column. The products were further

identified by  $^1\text{H}$  and  $^{13}\text{C}$  NMR (Varian-Gemini 300, tetramethylsilane,  $\text{CDCl}_3$ ) and FTIR.

Isatin ketal **2**, (*Spiro*[1,3-dioxolane-2,3'-indol]-2'(1'H)-one):  $\text{C}_{10}\text{H}_9\text{NO}_3$ . MS (70 eV): 191 (12), 163 (100), 146 (4), 136 (4), 119 (57), 104 (6), 92 (25), 76 (8), 64 (7). IR ( $\text{cm}^{-1}$ ): 3428, 3213, 3115, 2896, 2848, 1747, 1624, 1474, 1218, 1087, 760, 622, 486.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 65.8; 102.4; 110.8; 123.2; 124.3; 125.0; 131.6; 141.8; 175.8.

5-Chloroisatin ketal **4**, (*5'-Chloro-spiro*[1,3-dioxolane-2,3'-indol]-2'(1'H)-one):  $\text{C}_{10}\text{H}_8\text{NClO}_3$ . MS (70 eV): 227 (6), 225 (17), 197 (100), 180 (4), 166 (2), 153 (58), 138 (6), 126 (15), 110 (4). IR ( $\text{cm}^{-1}$ ): 3425, 3186, 3145, 3054, 2888, 1747, 1624, 1476, 1217, 1028, 990, 946, 814, 761, 643, 532.

Consecutive reaction runs were performed in order to investigate the repeated use and deactivation of the catalysts. After the first reaction run ( $t = 30$  min), the catalysts were centrifuged and transferred into the reactor recharged with fresh substrate and allowed to react. Additionally, the catalysts were washed with dichloromethane to remove residual reactants and products and then used in a next reaction run. FTIR spectra were collected for the fresh, used and washed catalysts.

The ketal yield was calculated as

$$Y(\%) = \frac{n(\text{ketal})}{n_0(\text{isatin})} \times 100$$

where  $n$  is the number of moles of produced ketal and  $n_0$  is the number of isatin moles at the starting time.

### 3. Results and discussion

#### 3.1. Characterization

The FTIR spectra collected for the heteropolyacid catalysts, HPW, HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW, showed the absorption bands assigned to the Keggin anion, confirming that it was not affected either by the impregnation procedure or by partial exchange of H<sup>+</sup> for Cs<sup>+</sup> ions during the preparation of the salt: P–O stretching (1080  $\text{cm}^{-1}$ ), W=O (985  $\text{cm}^{-1}$ ) and W–O–W (807 and 887  $\text{cm}^{-1}$ ) inter- and intratrimer stretchings, respectively [17,18]. A shoulder of silica band also appeared at approximately 1200  $\text{cm}^{-1}$  partially superseding the HPW 1080  $\text{cm}^{-1}$  stretching [13].

The X-ray diffraction patterns of HPW and Cs<sub>2.2</sub>HPW closely correspond to those reported in the literature, with the major lines at  $2\theta = 10.4^\circ$ ,  $26.0^\circ$  and  $30.5^\circ$ . For HPW/SiO<sub>2</sub>, the broadening of the peaks, as compared to those collected for HPW, could be assigned to HPW crystallites finely dispersed at the silica surface, as interpreted by Blasco et al. [19] or even to amorphous HPW without interactions with the silica support, as suggested by Pizzio et al. [10].

Four main weight loss peaks were found during the thermodesorption of cyclohexylamine: below 150 °C, due to physisorbed water and cyclohexylamine; 150–280 °C, corresponding to six crystallization water molecules per Keggin unit; 280–480 °C, assigned

to cyclohexylamine desorbed from acid sites of moderate strength and 500–670 °C, assigned to cyclohexylamine desorbed from strong acid sites. Above 400 °C, the decomposition of the Keggin unit occurred with total loss of protons, corresponding to a weight loss of 1.5 H<sub>2</sub>O molecules per Keggin unit [20]. Apparently, the strength of the acid sites of HPW was not affected by the impregnation and cation exchange procedures, respectively used for the preparation of HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW catalysts.

These results were corroborated by the NH<sub>3</sub> TPD profiles. The well-defined desorption peaks occurring at 630 and 590 °C, respectively for HPW and Cs<sub>2.2</sub>HPW, closely correspond to the weight loss peak (500–670 °C) assigned to the decomposition of the Keggin unit and were also attributed to the decomposition of the salt (NH<sub>4</sub>)<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> formed upon the adsorption of NH<sub>3</sub> on the strong acid sites of the heteropolycompounds [21]. On the other hand, the HPW/SiO<sub>2</sub> catalyst presented two broad NH<sub>3</sub> desorption peaks centered at 270 and 510 °C, suggesting that the surface acid strength is widely distributed [22] and that NH<sub>3</sub> was adsorbed on the silanol groups (SiOH).

In order to further confirm the above assumptions, the amount and the strength of acid sites was determined by potentiometric titration. According to Vásquez et al. [12], the potentiometric titration with 0.05 M *n*-butylamine enables the quantitative determination of Brønsted acid sites. As suggested by the author, sites at potential > 100 mV are very strong, sites at mV 0 < E < 100 are strong and those at –100 < E < 0 are weak. Acidic protons of the samples were very strong. The silica support was titrated at lower potentials (E < 0 mV), in the range of very weak acid sites, and it was assumed that they do not affect the catalytic properties of the impregnated HPW.

The amount of acid sites and the NH<sub>3</sub> TPD data are collected in Table 1 along with the surface area and pore volume of the catalyst samples. The amount of acid sites as determined by TG analysis of adsorbed cyclohexylamine was closely confirmed by potentiometric titration of the catalysts with *n*-butylamine and these figures were thus used to determine the amount of catalyst to be loaded for the reaction runs. In addition, the amount of ammonia desorbed at  $T_d$ , confirmed that the Keggin unit was preserved after the preparation procedures.

Much higher surface areas were determined for both HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW catalysts, either due to dispersion or lattice expansion due to H<sup>+</sup> exchange for Cs<sup>+</sup>. This behavior has been previously reported by Kozhevnikov [8].

#### 3.2. Reactions studies

In many syntheses using isatin derivatives, the more electrophilic carbonyl (on C3) is protected to allow the selective nucleophilic attack on the amidic carbonyl (on C2). This is usually accomplished preparing a ketal 1,3-dioxolane. The ketalization of isatin make it more lipophilic, thus increasing its pharmacology action [23].

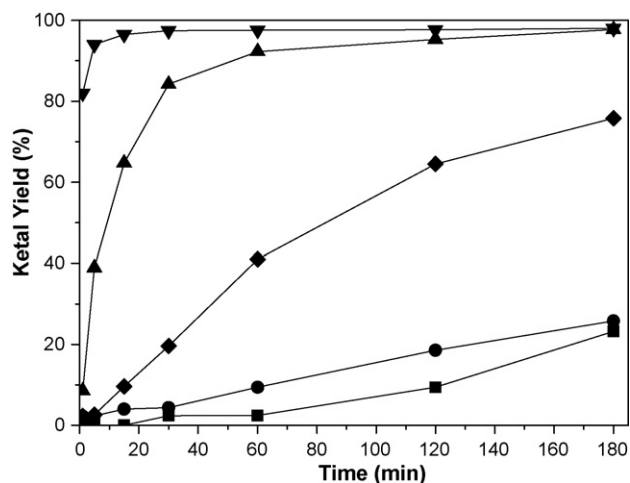
**Table 1**  
Surface area, pore volume and number of acid sites

Catalyst	BET surface area ( $\text{m}^2 \text{g}^{-1}$ )	Pore volume ( $\text{cm}^3/\text{g}$ )	Acid sites <sup>a</sup> ( $\text{mmol g}^{-1}$ )	Acid sites <sup>b</sup> ( $\text{mmol g}^{-1}$ )	$T_d^c$ (°C)
HPW	3.4	0.01	0.91	0.91	630
HPW/SiO <sub>2</sub>	233.0	0.39	0.35	0.37	270 and 510
Cs <sub>2.2</sub> HPW	105.3	0.13	0.26	0.25	590
SiO <sub>2</sub>	392.2	0.74	–	0.07	–

<sup>a</sup> Cyclohexylamine thermodesorption.

<sup>b</sup> Potentiometric titration with *n*-butylamine.

<sup>c</sup> NH<sub>3</sub> TPD.



**Fig. 1.** Isatin ketalization: 100 mg (0.68 mmol) of isatin, 100 mg of HPW (0.033 mmol; 0.091 mmol of  $H^+$ ) and 2 mL (33 mmol) of ethyleneglycol at 23 °C (■), 30 °C (●), 45 °C (◆), 60 °C (▲) and 100 °C (▼).

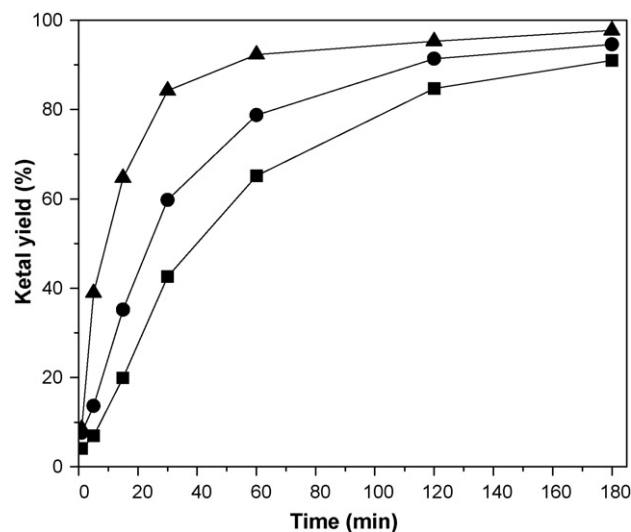
The isatin conversion in the presence of HPW catalysts is shown in Fig. 1, at different reaction temperatures.

The used isatin:HPW molar ratio was 1:0.05, corresponding to an isatin:acid sites molar ratio of 1:0.13, and ethyleneglycol (33 mL) was used in excess in order to avoid the use of solvents. Inasmuch as the reaction is reversible, ketal production is favored in excess of this reagent.

In a typical procedure to produce cyclic ketals, a dialcohol, usually ethyleneglycol; *p*-toluenesulphonic acid, as catalyst, and toluene or benzene, as solvent, were used, followed by water removal by Dean-Stark distillation. The dioxolane ketal of isatin could be thus obtained with 83% yield, after 6 h [5]. Nevertheless, this procedure used a homogeneous catalyst, toxic solvents and requires long reaction time and additional separation and neutralization steps.

As shown in Fig. 1, at 100 °C, 96.5% isatin conversion to ketal was attained in 15 min. The dissolution of isatin in ethyleneglycol favors the reaction and is enhanced by heating. The temperature increase also favors the shift of equilibrium toward the ketal production.

The results presented in Fig. 1 are much better than those reported using similar amount of *p*-toluenesulphonic acid as catalyst [5] and no special separation step was required but a dichloromethane extraction to separate the ketal from the reaction mixture.



**Fig. 2.** Isatin ketalization: 100 mg of isatin (0.68 mmol), 2 mL of ethyleneglycol (33 mmol) and HPW: 25 mg (0.008 mmol; 0.023 mmol of  $H^+$ ) (■), 50 mg (0.017 mmol; 0.046 mmol of  $H^+$ ) (●) and 100 mg (0.033 mmol; 0.091 mmol of  $H^+$ ) (▲) at 60 °C.

After 12 h, the ketal yields were 77, 82, 99.1 and 99.2%, at 23, 30, 60 and 100 °C, respectively. Even after a 12-h reaction run, no ketal hydrolysis product could be identified. The ketal yields were 2.14% and 43.5%, respectively at 30 and 100 °C, after 12 h reaction runs using the same amount of isatin and ethyleneglycol, without catalyst. No conversion depression was observed due to water by-product and hydrolysis products were not detected.

The influence of the amount of catalyst on the isatin ketalization conversion at 60 °C is shown in Fig. 2. Using a molar ratio isatin:HPW = 1:0.012 (25 mg HPW), corresponding to molar ratio isatin:acid sites = 1:0.03, the isatin ketal yield was higher than those reported for the previously described conventional procedure [1,5]. The ketal yield attained 96.4% after 1 h reaction run at 100 °C, using 25 mg HPW. These figures were interpreted as an evidence of the superacid character of the Keggin heteropolyacids [9].

In spite of the promising results achieved using HPW, a homogeneous catalyst, reaction runs were performed using the HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW heterogenized catalysts, in order to further improve the ecofriendly character of the studied isatin ketalization method. The experimental conditions and results of these reaction runs are collected in Table 2.

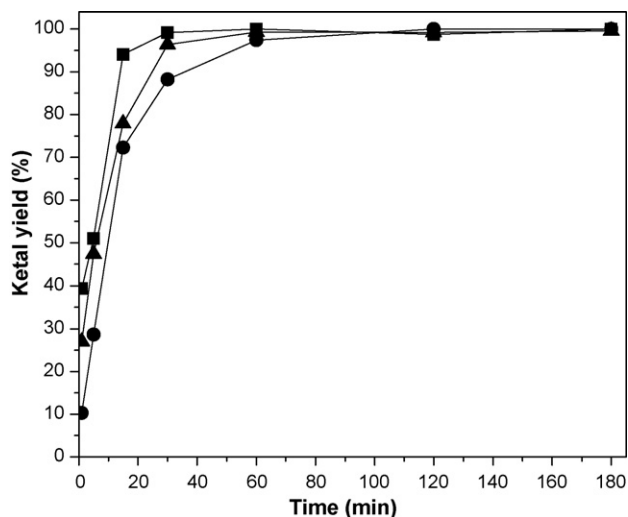
**Table 2**

Isatin ketalization in the presence of HPW, HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW catalysts

Catalyst	Isatin:acid sites (molar ratio)	TON <sup>a</sup> (h <sup>-1</sup> )	Time (min)	Temperature (°C)	Yield <sup>b</sup> (%)
HPW	1:0.13	83	1	60	18.5
			120	60	95.3
HPW/SiO <sub>2</sub>	1:0.13	59	1	60	13.0
			120	60	95.2
Cs <sub>2.2</sub> PW	1:0.13	85	1	60	18.9
			120	60	95.9
HPW	1:0.03	764	1	100	42.6
			120	100	97.5
HPW/SiO <sub>2</sub>	1:0.03	410	1	100	22.1
			120	100	97.6
Cs <sub>2.2</sub> PW	1:0.03	739	1	100	39.8
			120	100	98.0

<sup>a</sup> Turnover number (TON) calculated as mmol isatin/mmol  $H^+$ , at 1 min.

<sup>b</sup> No side reaction was observed.



**Fig. 3.** Ketalization of 5-chloroisatin: 123 mg of 5-chloroisatin (0.68 mmol), 2 mL of ethyleneglycol (33 mmol) and 25 mg of HPW (0.023 mmol of H<sup>+</sup>, ■), or 85 mg of Cs<sub>2.2</sub>HPW (0.022 mmol of H<sup>+</sup>, ●) or 63 mg of HPW/SiO<sub>2</sub> 40% (0.022 mmol of H<sup>+</sup>, ▲).

The results presented in Table 2 indicate that both of HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW catalysts are active for the isatin ketalization reaction. The equilibrium was attained after 2 h, at 60 and 100 °C, with yields varying around 95 and 98%, respectively. Acid solids, such as sulfated zirconia, zeolites and clays, have also been reported as useful ketalization catalysts but the high ketal yields reported herein were obtained using a lower substrate/catalyst mole ratio [24].

As the dioxolane ketal of 5-chloroisatin **4** presents significant anticonvulsant and anxiolytic activities, the heteropolyacid catalysts were also tested for the ketalization of 5-chloroisatin **4** and the results are shown in Fig. 3.

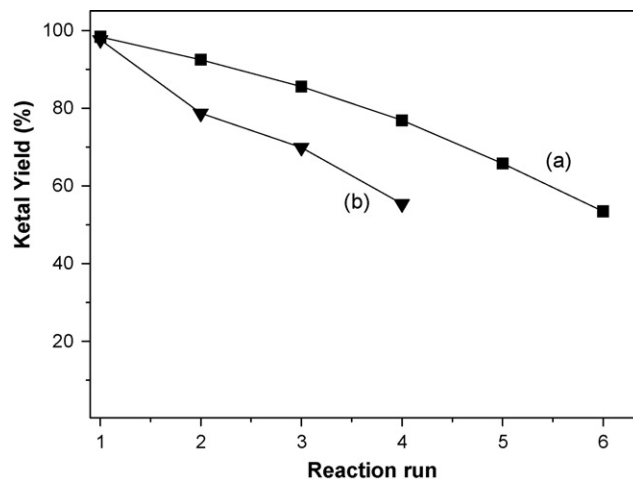
After 1 h reaction runs, the ketal yields obtained in the presence of for HPW, HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW catalysts were 100, 99.3 and 97.4%, respectively. As expected, these yield values were even higher than those obtained for the ketalization of isatin, at similar reaction conditions. The nucleophilic attack to a carbonyl is favored by the electrophilic character of the carbon atom on it. Indeed, the ketalization of isatin bearing electron-withdrawing groups, such as chlorine, should be favored as compared to isatin [5].

Taking into account that the number and strength of the acid sites on the catalysts were not changed (Table 2), these high ketal yields could be interpreted as an indication of the accessibility to the acid sites in the pore system of the solid catalysts.

In spite of this, HPW leaching experiments were carried out in order to determine the contribution of homogeneous reaction to the obtained yields. Using the same reaction conditions, samples of the liquid phase were periodically collected and analyzed by UV–vis. The collected spectra of the liquid phase showed that HPW was almost instantaneously leached from the silica support in the reaction slurry, around 80% in the initial minute, at 23 °C. This intensive HPW leaching in ethyleneglycol should be expected because of the high solubility of the heteropolyanion in polar solvents and the consequent higher affinity for the polar reaction media than for the surface of the silica support. These findings thus indicated that the reaction is homogeneously catalyzed in the presence of HPW/SiO<sub>2</sub> and confirmed the heterogeneous character of the Cs<sub>2.2</sub>HPW catalyzed reaction.

### 3.3. Reuse and deactivation studies

An environmentally friendly catalyst should be repeatedly used with sustained activity and selectivity [25]. The leaching tests



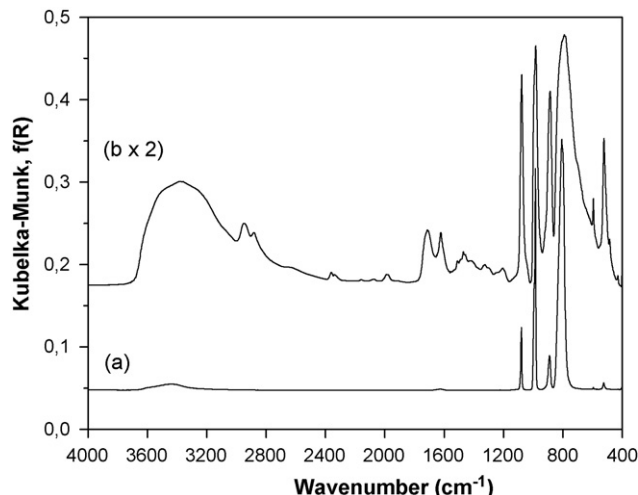
**Fig. 4.** Repeated use of the Cs<sub>2.2</sub>PW catalyst: (a, ■) dichloromethane extraction and (b, ▲) direct reuse, without extraction.

showed that HPW/SiO<sub>2</sub> is not useful as heterogeneous catalysts then reuse and deactivation studies were undertaken using the Cs<sub>2.2</sub>PW catalyst.

The repeated use of the Cs<sub>2.2</sub>PW catalyst, up to six reaction runs, is shown in Fig. 4. A yield decrease was observed when the catalyst was directly reused after centrifugation (Fig. 4b). In fact, after use, the catalyst became yellow colored after use, suggesting that any residual material was deposited onto the surface, accounting for the observed yield decrease.

Thus, before each reuse, the catalyst was washed up with dichloromethane, typically with five portions of 10 mL of dichloromethane, until no reaction residual compounds could be further extracted and detected by GC. A progressive but slower yield decrease was still observed, as shown in Fig. 4a.

In order to investigate these last findings, DRIFT spectra of the fresh Cs<sub>2.2</sub>PW catalyst (a) and of the catalyst after five washings with dichloromethane (b) were collected and are shown in Fig. 5. Both spectra show the bands assigned to the Keggin unit, indicating that it was not affected during the reaction. However, in the spectra of the used and washed Cs<sub>2.2</sub>PW catalyst (Fig. 5b), these bands are combined with bands assigned to isatin and ketals. This confirmed the presence of firmly adsorbed residual compounds that could not



**Fig. 5.** FTIR spectra for (a) fresh and (b) used and washed catalysts.

be removed from the catalyst by extraction with dichloromethane and that apparently accounted for the observed yield decrease.

#### 4. Conclusion

Isatin ketals were successfully prepared using HPW and  $\text{Cs}_{2.2}\text{H}_{0.8}\text{PW}_{12}\text{O}_{40}$  ( $\text{Cs}_{2.2}\text{HPW}$ ) as catalysts. High yields and 100% selectivity were attained using low isatin:acid sites molar ratios.

The heterogenization of the soluble HPW by impregnation on silica was not operative due to the intensive HPW leaching in the reaction slurry, rendering a significant homogeneous contribution to the reaction yield.

Among the tested catalysts,  $\text{Cs}_{2.2}\text{HPW}$  seems to be the most promising, since it is insoluble reaction medium, insensitive to the presence of water in the highly polar reaction media and fairly reusable, in spite of a slow but progressive yield decrease due to firmly adsorbed residual compounds. Additionally, the heterogeneous catalyst derived from Keggin heteropolyacids is an environmentally friendly alternative to conventional homogeneous and low selectivity acid catalysts, such as aluminum chloride and sulfuric acid. The present methodology also offers high yields, 100% selectivity and easy products separation of fast and solvent free reactions.

#### Acknowledgment

The authors are thanked to CNPq for the financial support.

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