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## Synthesis of enantiomerically pure aryl, hetero aryl and alkyl sulfinimides catalyzed by recyclable tungstophosphoric acid



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### ABSTRACT

A simple and efficient procedure was developed for the preparation of a variety of aryl, hetero aryl and alkyl N-sulfinylimines (**2b-2u**) with excellent yields (85–94%) using tungstophosphoric acid as catalyst. Also, this new synthetic protocol features high conversion, shorter reaction time, a straight forward and simple work up procedure. Catalyst was recycled for 10 times without much loss in activity and also scaled up in gram level with high yield. Hence, it is highly applicable for the industrial scale up process.

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### 1. Introduction

Enantiomerically pure aldsulfinimides are important building blocks for the synthesis of a number of biologically active molecules [1,2], chiral amines [3–7], aziridines [8–10] and  $\alpha$ - and  $\beta$ -aminophosphonic acids [11,12]. Though there are reports on the synthesis of aldimines [13–16], most of them have their own disadvantages such as use of stoichiometric, expensive reagents, harsh conditions, less yield and longer reaction time. Furthermore, titanium tetraethoxide mediated imine formation is the choice of most of the reactions reported so far. But the drawback of this particular reagent is the removal of titanium salt during the work up and also stoichiometric quantity used [13]. Yet, other reagents are also used for the aldimine formation such as metal based reagents or catalysts [14,15]. Recently, an effective method was developed by Reeves et al., wherein they use tris (2, 2, 2-trifluoroethyl) borate as reagent [16] for both aldimines and ketimines. But, it requires the use of very expensive and stoichiometric amount of reagent.

Chemical and pharmaceutical industries are forced to reduce the overall manufacturing cost in addition to environmentally benign synthetic procedure due to global competitiveness and stringent regulations enforced by the Environmental Protection Agencies (EPA's). Heteropoly acids (HPAs) are solid acids which are employed as homogenous and heterogeneous catalyst [17]. Interestingly, HPAs in solution are found to be stronger than the mineral acids such as  $H_2SO_4$ , HCl,  $HNO_3$ , etc., [18]. Furthermore, HPAs have significant properties like less toxic, suitable to handle in any quantity, environmentally benign character, cost effectiveness and commercial availability [19]. Among the many available acids, keggin's HPAs are more stable and readily employable (tungstophosphoric acid (TPA), phosphomolybdic acid (PMA), silicotungstic acid (STA)) [20,21].

Furthermore, a clean, high yielding, recyclable, optically pure and scalable method would offer many advantages such as operational simplicity and less wastage generation. Usage of recyclable catalyst is more favored in industries due to its economic viability, easy separation and less wastage generation. Hence, we herein wish to report a simple and efficient process for the preparation of aryl, hetero aryl and aliphatic aldimines in the presence of tungstophosphoric acid as catalyst. To the best of our knowledge, the use of the TPA as catalyst for synthesis of aldsulfinyl imines has not been reported so far.

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**Table 1**  
Effect of amounts of TPA and other catalysts on the synthesis of (S)-**2a** by the reaction of benzaldehyde (**1a**), with (S)-*t*-butylsulfinamide ((S)-**3**).

Entries	Catalyst	Substrate/Amine /Cat. (Equiv.)	Time (h)	Temp (°C)	Isolated yield (%) <sup>c</sup>
1	SPEEK/TPA (A) <sup>a</sup>	1:1.2:40 <sup>b</sup>	24	rt	90
2	SPEEK/TSA (B) <sup>a</sup>	1:1.2:40 <sup>b</sup>	24	rt	87
3	H <sub>4</sub> SiW <sub>12</sub> O <sub>40</sub> nH <sub>2</sub> O (C)	1:1.2:0.2	20	rt	80
4	H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (D)	1:1.2:0.2	12	rt	93
5	H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (D)	1:1.2:0.1	1	60	93
6	H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (D)	1:1.2:0.01	2	60	92
7	Zeolite ZSM-5 (E)	1:1:20 <sup>b</sup>	2	60	60
8	Amberlite <sup>®</sup> IR120 hydrogen form (F)	1:1:20 <sup>b</sup>	2	60	75
9	Montmorillonite (G)	1:1:20 <sup>b</sup>	2	60	70
10	Aluminium silicate (H)	1:1:20 <sup>b</sup>	2	60	48

<sup>a</sup> SPEEK – Sulfonated poly (ether ether ketone).

<sup>b</sup> 40 and 20 represent the wt% with the starting material.

<sup>c</sup> The products were purified by column chromatography on silica gel (230–400 mesh, EtOAc – petroleum ether, 9:1).

## 2. Experimental section

Unless otherwise stated, all reactions were performed in flame-dried glassware under an atmosphere of N<sub>2</sub>. All chemicals and reagents such as aldehydes, (S)-*t*-BuSONH<sub>2</sub>, (RS)-*t*-BuSONH<sub>2</sub>, phosphotungstic acid, tungstosilicic acid, zeolite ZSM-5 (SiO<sub>2</sub>:Al<sub>2</sub>O<sub>3</sub> = 50:1), amberlite<sup>®</sup> IR120 hydrogen form, montmorillonite K10 and aluminium silicate (3Al<sub>2</sub>O<sub>3</sub> · 2SiO<sub>2</sub>) were purchased from Aldrich and Alfa Aesar suppliers and used without further purification. Flash column chromatography was performed with silica gel (230–400 mesh size). Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm); detection was accomplished using a UV254 light and staining with phosphomolybdic acid staining solution; NMR data was recorded on a Bruker 500 MHz spectrometer, operating at 500 MHz for <sup>1</sup>H acquisitions in the indicated deuterated solvent. Chemical shifts (δ) are reported in parts per million (ppm) and relative to TMS at 0 ppm. The data is reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz). HPLC analysis was performed on a Shimadzu prominence UFLC binary gradient HPLC system. Conversion was determined by the HPLC using analytical C<sub>18</sub> column. The enantiomeric purities (% e.e.) of **2b** and **2l** were determined by chiral HPLC analysis in comparison with racemates. The column used was Chiralpak<sup>®</sup> AD-H LC column 250 × 4.6 mm. The mobile phase was hexane – isopropanol at a flow rate of 0.4 mL min<sup>-1</sup> and the absorbance was monitored using a UV detector at 254 nm.

### 2.1. Synthesis of sulfonated poly (ether ether ketone) (SPEEK)

The sulfonation of poly (ether ether ketone) (PEEK) was performed according to the reported literature [25,26]. The powdered form of PEEK was first dried in a vacuum oven at 100 °C for 24 h. A volume of 100 mL of conc. sulfuric acid was taken in a round bottom flask and heated up to 40 °C in a water bath fitted in a magnetic stirrer. A quantity of 2.0 g of dried PEEK was slowly transferred to the acid for the period of 1 h. The reaction mass was constantly stirred and maintained at 50 °C for 5 h. The obtained viscous solution was slowly transferred to the beaker containing large excess of ice-water. The resultant pink colored solid was filtered and washed thoroughly with de-ionized water until the neutral pH reached. The resulted sulfonated PEEK was dried at 100 °C for 12 h in a vacuum oven.

### 2.2. Preparation of SPEEK – Heteropoly acids (HPA) composite membranes

The acid form of 5 wt% SPEEK polymer was dissolved in N, N-dimethylacetamide with constant stirring using a magnetic stirrer. After the whole dissolution of SPEEK, 20 wt% heteropoly acids (sil-

icotungstic acid and phosphotungstic acid) was added, stirred well and heated up to 60 °C for 6 h. After that the viscous polymer solution was cast onto a flat glass plate using a thin glass rod and was kept in a closed chamber for 24 h. The cast membranes were dried at 60 °C for 6 h, 90 °C for 8 h and 140 °C for 3 h. The resultant dried films were soaked in de-ionized water overnight to release the membranes from the glass plates. Then the composite membranes were carefully washed with de-ionized water and dried in a vacuum oven at 100 °C for 12 h. The infra-red absorption bands of W–O–W and W=O vibrations for HPA were obtained at 895 cm<sup>-1</sup> and 980 cm<sup>-1</sup> respectively. These characteristic absorptions confirm the successful incorporation of the tungstic acid in to the SPEEK polymer.

### 2.3. Synthesis of

(E)-*N*-benzylidene-2-methylpropane-2-sulfinamide (**2b**) using SPEEK/heteropoly acids (HPA or STA) or STA or TPA

To a stirred solution of benzaldehyde **1** (2 mmol) in toluene (5 mL) was added 2-methyl-2-propanesulfinamide (**3**; 2.4 mmol) under inert conditions. Catalysts A or B (40 wt%) and catalysts C or D (as mentioned in Table 1) was added and the reaction mixture was heated to 60 °C for 2–4 h. Progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to room temperature. Crude reaction mixture was filtered and then washed with toluene. The solvent was evaporated under reduced pressure to obtain a crude mass, which was purified by flash chromatography on silica gel using hexanes–EtOAc as eluent to afford pure compound **2a**.

### 2.4. Recyclability test on PTA for the synthesis of

(E)-*N*-benzylidene-2-methylpropane-2-sulfinamide (**2b**)

To a stirred solution of benzaldehyde **1a** (2 mmol) in toluene (5 mL) was added 2-methyl-2-propanesulfinamide (**3**; 2.4 mmol) under inert conditions in a 10 mL screw capped vial. TPA (1 mol%) was added and the reaction mixture was heated to 60 °C for 2–6 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to room temperature and then filtered through a sintered crucible and washed with toluene (2 × 2 mL). The solvent was evaporated under reduced pressure to obtain a crude compound, which was purified by flash chromatography on silica gel using hexanes–EtOAc as eluent to obtain compound **2a**. Recovered catalyst was reused by following the same procedure. The reaction was repeated using recovered catalyst for 10 subsequent cycles. Yields ranged from 90 to 92%.

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