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Novel Synthesis of 1,5-Benzodiazepines Catalyzed by Silica-Supported Dodecatungstophosphoric Acid

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Abstract

Silica supported 12-tungstophosphoric acid catalyzes efficiently the reaction of *o*-phenylenediamines with ketones under solvent-free condition to afford the corresponding 1,5-benzodi-azepines in good yields. The catalyst can be recovered by simple filtration and reused.

Introduction

The compounds with 1,5-benzodiazepine scaffold have recently received considerable attention because of their pharmacological properties.[1] Many members of benzodiazepines are widely used as antianxiety, analgestic, sedative, antidepressive and hypnotic agents.[2] These compounds also find commercial use as dyes for acrylic fibers[3] and as anti-inflammatory agents.[4] In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring compounds such as triazolo-[5] and oxadiazolo-benzodiazepines.[6]

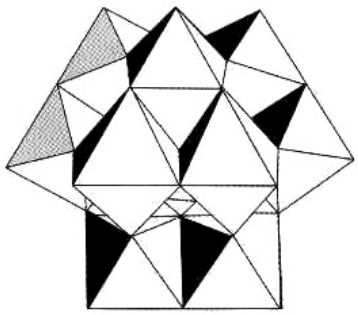
The general and simplest method for synthesis of 1,5-benzodiazepines involves the acid catalyzed reaction of *o*-pheneylenediamine with ketones, β-haloketones and α,β-unsaturated carbonyl compounds. Many catalysts have been reported in the literature for this reaction including BF_3-OEt_2,[7] polyphosphoric acid-SiO_2,[8] $NaBH_4$,[9] $MgO/POCl_3$,[10] $Yb(OTf)_3$,[11] CH_3COOH using microwave,[12] SO_4^{2-}/ZrO_2[13] and Al_2O_3-P_2O_5.[14]

Chemical processes often employ large amounts of hazardous and toxic solvents. The choice of pursuing a low-waste route and reusable reaction media to minimize the economic cost and

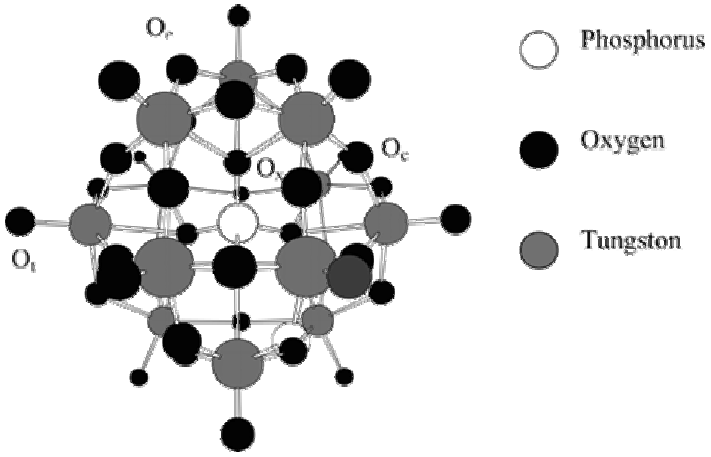
environmental impact of a chemical process is becoming ever more urgent for the future, so there is pressure on organic chemists to investigate clean, economical, and environmentally safer methodologies. Due to wide range of biological application of 1,5-benzodiazepines, the development of efficient, clean and environmentally friendly protocols for the synthesis of 1,5-benzodiazepines are desirable.

Results and Discussion

The application of solid acid catalysts and especially supported solid acids have received considerable importance in organic transformation because of their ease of handling, greater selectivity, simple workup and reusability of catalyst. Among the various solid acids, Heteroploy acids (HPAs) with keggin structure are widely used as solid acid catalysts due to their very strong Bronsted acidity and their structure properties.

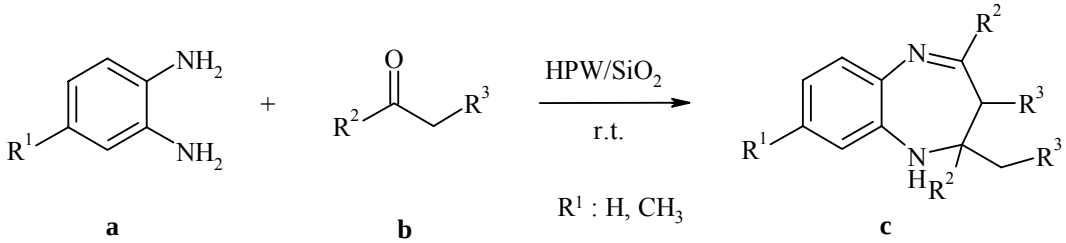


Keggin Unit primaty structure of HPA



Schematic diagram of the $PW_{12}O_{40}^{3-}$ Keggin anion

Herein, we wish to report the application of silica supported 12-tungstophosphoric acid (HPW/SiO_2) as solid acid catalyst for the synthesis of 1,5-benzodiazepines by reaction of phenylenediamines and with ketones (scheme 1).

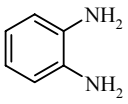
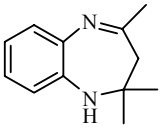
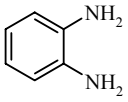
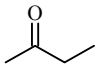
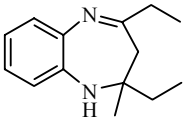
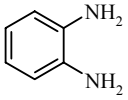
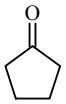
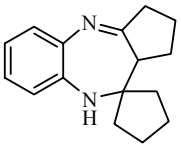
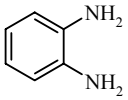
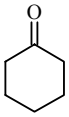
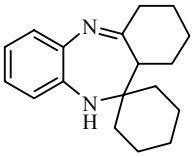
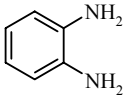
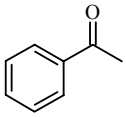
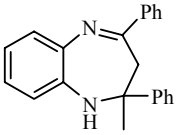
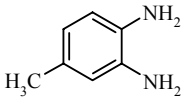
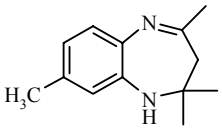
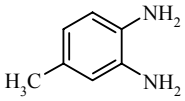
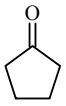
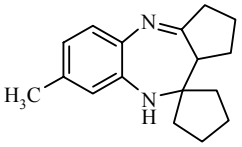
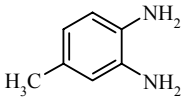
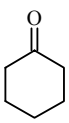
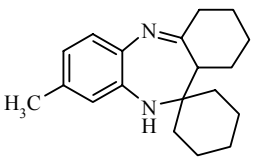


a **b** **c**

Scheme 1

Along this line, acetone and phenylenediamine were reacted in the presence of catalytic amount of HPW/SiO_2 (1 mol% catalyst per 1 mol diamine) at room temperature under solvent free condition which afforded 2,4,4-trimethyl-2,3-dihydro,1H-1,5-benzodiazepine in 92% yield. Similarly, different ketones were reacted with ethylenediamines under the same reaction conditions to give the corresponding 1,5-benzodiazepine derivatives in good yields (Table 1).

Table 1: silica-supported HPW catalyzed synthesis of 1,5-benzodiazepines

Entry	Diamine(a)	Ketone(b)	Benzodiazepine(c)	Time (min)	Yield (%)
1				20	92
2				160[b]	75
3				15	88
4				20	90
5				100[b]	87
6				20	86
7				15	87
8				20	85

[a]Isolated yields
[b]1.5 mol % catalyst

The reaction of cyclic ketones such as cyclohexanone and cyclopentanone with *o*-phenylenediamines afforded fused ring 1,5-benzodiazepines also in good yields. The progress of the reactions was monitored by TLC (eluant; EtOAc : *n*-Hexane 2-4 : 8-6). After completion of the reaction, the catalyst was easily separated by addition of ethyl acetate and simple filtration. All products were identified by comparing their spectral and physical data with authentic samples.

To show reusability of catalyst, the recovered catalyst from the reaction of cyclohexanone was used for the same reaction for three times. For any reaction, no appreciable change in activity was noticed.

EXPERIMENTAL

Catalyst preparation:

Silica-supported catalyst containing 30 wt. % $H_3PW_{14}O_3/SiO_2$ (HPW/SiO_2) was prepared by impregnating silica with an aqueous solution of HPW using 10 ml solution per gram of silica. The suspension was stirred overnight. The mixture was evaporated at 80 °C until dryness. The catalyst was then calcined in air at 150 °C for about 2 h.

General procedure for synthesis of 2,3-dihydro-1,5-benzodiazepines:

A mixture of *o*-phenylenediamine (1 mmol) and ketone (2.1 mmol) was stirred at room temperature in the presence of 30 wt. % HPW/SiO_2 (95 mg, 1 mol % HPW) for an appropriate time. The progress of the reaction was followed by TLC using 20%-40% EtOAc in *n*-Hexane as eluent. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (5 ml) and the catalyst was recovered by filtration. The organic layer was evaporated and crud products were purified by recrystalization in *n*-Hexane or by column chromatography by silica gel using EtOAc : *n*-Hexane 20 : 80 as eluent.

Selected data for compound **1c** are given: Mp 137-139 °C. IR (KBr): 3295, 1633, 1593 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 1.32 (s, 6 H), 2.20 (s, 2 H), 2.34 (s, 3 H), 2.94 (br s, 1 H, NH), 6.68-7.13 (m, 4 H).

CONCLUSION

In summary, we introduced a mild, convenient and efficient method for the synthesis of 1,5-benzodiazepines by the reaction of *o*-pheneylenediamine with ketones using HPW/SiO_2 as recyclable solid catalyst. The simple experimental procedure, mild reaction conditions and ease of recovery and reuse of catalyst are advantages of this method.

Acknowledgment

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