Communication

Alumina Supported 12-Tungstophosphoric Acid as an Efficient and Reusable Catalyst for Synthesis of 1,5-Benzodiazepines

Mohammad Abdollahi-Alibeik,[a]* Zahra Zaghaghi[a] and Iraj Mohammadpoor-Baltork[b]
[a]*Department of Chemistry, Yazd University, Yazd 89195-741, Iran*
[b]*Department of Chemistry, Isfahan University, Isfahan 81746-73441, Iran*

Alumina supported 12-tungstophosphoric acid catalyzes efficiently the reaction of *o*-phenylenediamine with ketones under solvent-free condition to afford the corresponding 1,5-benzodiazepines in good to excellent yields. The catalyst can be recovered and reused.

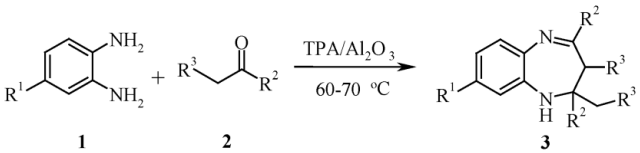
Keywords: 1,5-Benzodiazepine; *o*-Phenylenediamine; Alumina supported; Heteropoly acid; 12-Tungstophosphoric acid; Catalyst reusability.

INTRODUCTION

Benzodiazepines are an important class of biologically active compounds, widely used as analgesic, anti-anxiety, anticonvulsant, hypnotic, sedative and antidepressive agents.[1] In addition, some benzodiazepine derivatives are used as anti-inflammatory agents[2] and also as dyes for acrylic fibers.[3] Particularly, 1,5-benzodiazepines are valuable synthons for the preparation of some fused ring benzodiazepine derivatives.[4,5] Due to their wide range of pharmaceutical, industrial and synthetic applications, these compounds have received a great deal of attention. The simple and general method for the synthesis of 1,5-benzodiazepines involves the acid catalyzed condensation of *o*-phenylendiamines with ketones. A variety of catalysts such as $BF_3.OEt_2$,[6] $NaBH_4$,[7] $MgO\text{-}POCl_3$,[8] $PPA\text{-}SiO_2$,[9] $Yb(OTf)_3$,[10] $Al_2O_3\text{-}P_2O_5$,[11] HOAc-MW,[12] SO_4^{-2}/ZrO_2,[13] $Ag_3PW_{12}O_{40}$,[14] $Fe(ClO_4)_3$,[15] $HClO_4/SiO_2$[16] are utilized for this condensation reaction. However, the use of many of these catalysts are associated with several shortcomings such as application of expensive materials, drastic reaction conditions, extended reaction times, side products formation, low product yields and difficulty in recovery and reusability of the catalysts. Hence, there is a need to develop a convenient, efficient and practically useful protocol for the synthesis of 1,5-benzodiazopines. In recent years, the use of solid acid catalyst has received considerable attention in organic transformations. This is mainly due to the advantages of solid acid catalysts such as non-toxicity, non-corrosiveness, less expensive, ease of handling, recovery and reusability.[17] Among the various types of solid acids, heteropoly acids such as 12-tungstophosphoric acid (TPA) are well known to passes purely Brønsted acidity and have been widely used in some acid-catalyzed reactions.[18] However, pure heteropoly acids generally show very low catalytic reactivity owning to their very poor surface area. Therefore, immobilization of heteropoly acids on the surface of porous solids, are more effective for catalytic reactions.[19] In this regards, deposition of heteropoly acids on basic solids like MgO and Al_2O_3 prevents its dissolution in polar solvents and reagents due to strong chemical bonding.[20] In spite of their advantages, comparatively few reports for the application of alumina supported heteropoly acid are reported in the literature.

In this communication, we wish to report efficient synthesis of 1,5-benzodiazepines by the reaction of *o*-phenylenediamines with ketones in the presence of catalytic amounts of alumina supported 12-tungstophosphoric acid (Scheme I).

Scheme I



1 **2** **3**

R^1, R^2, R^3 = H, alkyl, aryl

* Corresponding author. E-mail: abdollahi@yazduni.ac.ir

RESULTS AND DISCUSSION

Initially, the supported 12-tungstophosphoric acid catalysts were prepared by impregnation method with concentration depending upon the loading required to the support. The reaction of *o*-phenylenediamine with acetophenone was performed using different TPA loaded (20-60 wt.%) catalysts and the results are presented in Table 1. It is seen that 1,5-benzodiazepine formation increased with increase in TPA loading up to 40 wt.% and decreased further with increase in loading. However, the 30 wt.% catalyst was chosen because of less leaching of heteropoly acid.

The effect of catalyst concentration was also investigated in the same reaction. It was found that 1.5 mol% of heteropoly acid relation to *o*-phenylenediamine shows the most activity, better reusability and less leaching of heteropoly acid. To show efficiency of the support, the reaction in the presence of pure heteropoly acid was performed and low yield of product was achieved. As shown in Table 1 the reaction in the presence of pure alumina and neat condition was performed and no reaction was observed.

Along this line, the reaction of acetone and *o*-phenylenediamine was performed in the presence of catalytic amount of TPA/Al_2O_3 (1.5 mol% of 30 wt.% catalyst per 1 mol *o*-phenylenediamine) at 60-70 °C under solvent-free condition which afforded 2,4,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (**3a**) in 92% yield. Accordingly, other types of ketones and *o*-phenylenediamines were reacted in the same reaction conditions and corresponding 1,5-benzodiazepines were achieved in high yields (Table 2).

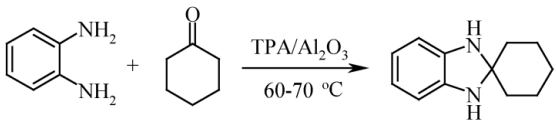
Table 1. Reaction of acetophenone with *o*-phenylenediamine in the presence of various catalysts

Entry	Catalyst	TPA[b]	Time (min)	Yield (%)[c]
1	20% TPA/Al_2O_3	1	100	70
2	30% TPA/Al_2O_3	1	100	85
3	40% TPA/Al_2O_3	1	100	86
4	50% TPA/Al_2O_3	1	100	75
5	60% TPA/Al_2O_3	1	90	70
6	30% TPA/Al_2O_3	0.5	150	80
7	30% TPA/Al_2O_3	1.5	90	88
8	30% TPA/Al_2O_3	2	80	82
9	TPA	1	70	60
10	Al_2O_3[a]	-	120	5
11	None	-	100	0

[a] 97 mg Al_2O_3 for 1 mmol *o*-phenylenediamine was used.
[b] Mole ratio relative to *o*-phenylenediamine.
[c] Isolated yield.

The reaction of cyclopentanone with *o*-phenylenediamines also afforded corresponding fused ring 1,5-benzodiazepines in good yields (**3e, 3f**), whereas cyclohexanone was treated under similar conditions, gave only 2,3-dihydrobenzimidazole-2-spirocyclohexane (**3g**) (Scheme II). To the best of our knowledge there is only one report about different reaction products of cyclohexanone and cyclopentanone with *o*-phenylenediamine.[6] In this report BF_3-Et_2O has been used as catalyst for the reaction of ketones with *o*-phenylenediamines and in the case of cyclohexanone the corresponding spiro compounds has been achieved. However in our hands, the reaction of cyclohexanone with various *o*-phenylenediamines in the presence of TPA/Al_2O_3 was provided corresponding spiro compounds (**3g-3i**).

Scheme II

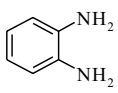
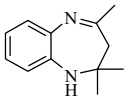
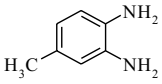
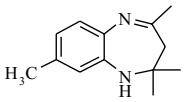
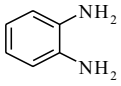
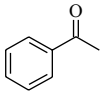
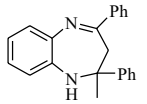
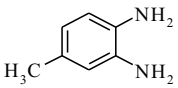
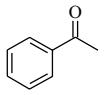
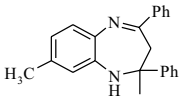
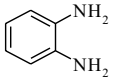
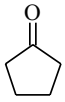
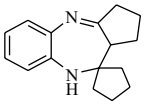
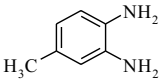
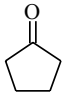
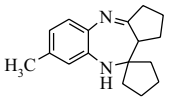
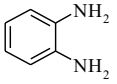
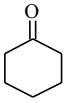
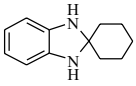
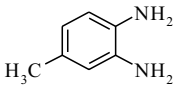
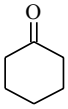
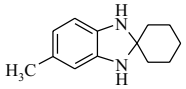
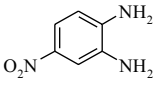
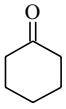
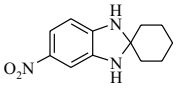


1 **2** **3**

Torsional strain plays a major role in different treatment of cyclic ketones with *o*-phenylenediamine. The products of the first step in these reactions are corresponding imines with different torsional strain and stability. It is observed that the reactions which convert a sp^2 carbon to sp^3 carbon in a six-membered ring are more favorable than the corresponding reaction in a five-membered ring.[21] This change in hybridization in a six-membered ring leads to a completely staggered arrangement and reduced torsional strain in the corresponding spiro compounds. Conversely, conversion of an sp^2 atom in a five-membered ring to sp^3, increases in the number of eclipsing interactions in the corresponding spiro compounds. Thus, after formation of the first imine intermediate from cyclohexanone and *o*-phenylenediamine, second amino group of diamine prefer to attack at sp^2 carbon of cyclic imine to produce spiro compounds, whereas, the corresponding imine of cyclopentanone is more stable and second amino group can attack to second cyclopentanone for production of diimine as intermediate of corresponding benzodiazepine.

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

Table 2. Alumina-supported TPA catalyzed reaction of *o*-phenylenediamines with ketones

Entry	Diamine (**1**)	Ketone (**2**)	Product (**3**)	Time (min)	Yield (%)[a]
a				30	91
b				30	88
c				50	88
d				55	90
e				40	90
f				40	89
g				40	93
h				45	88
i				50	95

[a] Isolated yields

identified by comparing their spectral and physical data with authentic samples.

To show reusability of the catalyst, the recovered catalyst from the reaction of cyclopentanone with *o*-phenylenediamine was used for the same reaction for three times. After each run the catalyst was washed thoroughly with acetone and dried in an oven at 120 °C for 1 h. For any reaction, no appreciable change in activity was noticed.

In summary, we introduced a mild, convenient and efficient method for the synthesis of 1,5-benzodiazepines by the reaction of *o*-pheneylenediamines with ketones using TPA/Al_2O_3 as recyclable solid catalyst. The simple experimental procedure, mild reaction conditions, ease of recovery and reuse of catalyst are advantages of this method.

EXPERIMENTAL SECTION

All chemicals were commercial products. All melting points were obtained by Buchi B-540 apparatus and are uncorrected. TLC monitored all reactions and all yields refer to isolated products. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker (DRX-500 Avance) 500 MHz spectrometer. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in cm^{-1}. Microwave irradiation was carried out in a Kenwood microwave oven, model MW303, operating at 800 W.

Catalyst preparation

Alumina-supported 12-tungstophosphoric acid (TPA)

containing 30 wt. % $H_3PW_{12}O_{40}/Al_2O_3$ (TPA/Al_2O_3) was prepared by impregnating alumina with an aqueous solution of TPA using 10 mL solution per gram of alumina. The suspension was stirred overnight. The mixture was evaporated at 80 °C until dryness. The catalyst was then calcined by irradiation in microwave oven (800 W) for 20 minutes.

General procedure for synthesis of 2,3-dihydro-1,5-benzodiazepines (3a-i)

A mixture of *o*-phenylenediamine (1 mmol) and ketone (2.1 mmol) was stirred at room temperature in the presence of 30 wt. % TPA/Al_2O_3 (95 mg, 1 mol % TPA) 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 crude product purified by recrystallization from *n*-hexane or by column chromatography on silica gel using EtOAc:*n*-hexane, 20:80 as eluent.

Physical and specteroscopic data for compounds 3c and 3i

***2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine* (3c):** mp 151-153 °C [Lit.[22] 152-154 °C]. IR (KBr): 3337 (NH), 1682 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H), 3.03 (d, 1H, *J* = 13.2), 3.19 (d, 1H, *J* = 13.2), 3.57 (br s, 1H, NH), 6.9-7.13 (m, 3H), 7.22-7.38 (m, 7H), 7.62-7.66 (m, 4H). ^{13}C NMR (^1H-decoupled): δ = 30.32, 43.51, 74.1, 121.84, 122.08, 125.86, 126.76, 127.51, 128.45, 128.74, 129.07, 130.162, 138.51, 140.04, 140.53, 148.05, 168.08.

***2,3-Dihydro-5-nitrobenzimidazole-2-spirocyclohexane* (3i):** mp 164-165 °C, [Lit.[23] 163-164 °C]. IR (KBr): 3375 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.48-1.84 (m, 10H), 4.15 (br s, 1H, NH), 4.69 (br s, 1H, NH), 6.37 (d, 2H, *J* = 8.4), 7.71 (d,d, 2H, *J* = 2.2). ^{13}C NMR (^1H-decoupled): δ = 23.50, 25.04, 39.83, 82.15, 103.35, 104.84, 119.80, 132.35, 140.62, 146.20.

ACKNOWLEDGEMENT

We are thankful to the Yazd University Research Council for support of this work.

Received August 8, 2007.

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