Wells-Dawson Type Catalyst: An Efficient, Recoverable and Reusable Solid Acid Catalyst for the Solvent-Free Synthesis of Benzodiazepines

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Abstract: Various 3-*H*-1,5-benzodiazepines were prepared from the solvent-free reaction of *o*-phenylenediamine and substituted 1,3-diphenyl-1,3-propanedione, giving good yields of benzodiazepines. The $H_6P_2W_{18}O_{62}.24H_2O$ solid heteropolyacid, which possesses a Wells-Dawson type structure was used as catalyst both in bulk and silica-supported forms (0.1, 0.2, 0.4 and 0.6 g/g, named $0.1WDSiO_2$, $0.2WDSiO_2$, $0.4WDSiO_2$ and $0.6WDSiO_2$, respectively). The structure of the synthesized heteropolyacid was confirmed using different characterization techniques (FTIR; ^{31}P-RMN, and potentiometric titration).

Keywords: Benzodiazepines, Green chemistry, Heterogeneous catalysis, Heteropolyacid, Solvent-free reaction, Wells-Dawson structure.

INTRODUCTION

Heterocyclic compounds are widely distributed in nature, and have an important pharmaceutical and biochemical role in living beings. Among the group of heterocyclic heptagonal molecules are benzodiazepines, bicyclic compounds which possess a benzene ring attached to a heptagonal heterocyclic ring with two nitrogen atoms in their structure. These compounds have been previously tested for their medical use as anxiolytic, anti-inflammatory, sedative, antidepressant [1], antifungal, and antibacterial agents [2]; benzodiazepines are also used as insecticides and herbicides [3-5], and as light-sensitive fibers in photography [6].

From 1907 until now, benzodiazepines have been synthesized by the condensation of *o*-phenyldiamines with acetylacetone (Scheme **1**) using different inorganic acid promoters. Due to the need for new environmentally friendly techniques in organic synthesis, in the last years various acid promoters have been tested on this reaction such as ytterbium triflate [7], indium tribromide [8], (bromodimethyl) sulfonium bromide [9], cerium chloride/ sodium iodide, phosphorous pentoxide/alumina [10], zinc montmorillonite [11], sulfated zirconia [12], p-nitrobenzoic acid [13], p-toluenesulfonic acid [14], sulfamic acid [15], polyphosphoric acid [16], acetic acid [17], samarium iodide [18] and MCM-22 zeolite [19]. One of the main topics in green chemistry is the use of catalysts capable of being recovered and reused; among the various possibilities are heteopolyacids (HPAs), a group of solid catalysts with superacidic properties. In this group is the HPA $H_6P_2W_{18}O_{62}.24H_2O$ with Wells-Dawson structure, a molecular arrangement with formula $[X_2M_{18}O_{62}]^{-m}$, formed by two XM_9O_{34} Keggin-type units where a WO_6 octahedron has been removed from each of the W_3O_{13} common group. Some silicotungstic acid salts were previously reported for benzodiazepine synthesis [20].

This type of HPA has been successfully used in acid catalyzed and oxidation reactions. For example, the synthesis of diverse phenylpropanoids such as coumarins [21], dihydrocoumarins [22] and flavones [23], the preparation of N-sulfonyl-1,2,3,4- tetrahydroisoquinolines [24], or the oxidation of isobutene [25], methacrolein, and benzyl alcohol [26], among others.

In this paper we report the synthesis of benzodiazepines using a Wells-Dawson catalyst supported on silica capable of being recovered and reused without loss of its activity, following some of the Green Chemistry principles, obtaining a good yield and environmentally compatible procedure.

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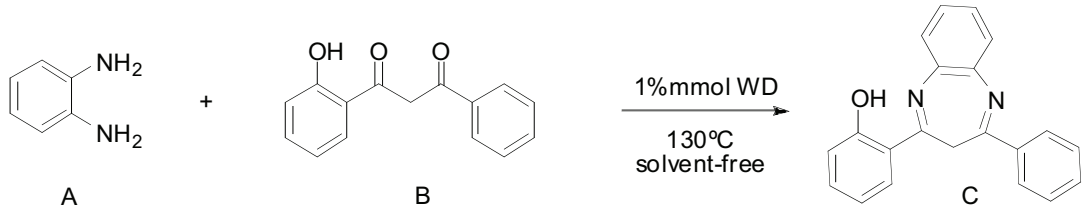


Scheme (1). 3-H-1,5-benzodiazepines synthesis**.**

MATERIALS AND METHODS

All the chemicals were purchased from Aldrich and used without further purification. Melting points were determined in open capillary tubes and were uncorrected. Thin layer chromatography (TLC) was performed on UV-active aluminum-backed plates of silica gel (TLC Silica gel 60 F254). ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker 200 MHz spectrometer in $CDCl_3$ with chemical shift given in ppm relative to TMS as internal standard.

Catalyst Preparation

The WD acid $H_6P_2W_{18}O_{62}.24H_2O$ was prepared by the Drechsel method from an α/β $K_6P_2W_{18}O_{62}.10H_2O$ isomer mixture as previously reported [21] from concentrated H_3PO_4 and aqueous solution of $Na_2WO_4.2H_2O$, in a reflux system for 8 h. The salt was then precipitated by adding KCl, then purified by recrystallization and cooled overnight to 278 K. The product was filtered, washed and then vacuum-dried for 8 h. The acid was obtained from an aqueous solution of α/β $K_6P_2W_{18}O_{62}.10H_2O$ salt treated with ether and concentrated HCl (37%) solution. After obtaining this solution, the ether was eliminated by flowing dry air and the remaining solution was placed in a vacuum desiccator until crystallization.

Silica-supported Wells-Dawson acid ($WDSiO_2$) was prepared by wet impregnation of Grace Davison silica (Grade 59, specific area = 250 m^2/g) with an aqueous solution of the synthesized WD acid. Various catalysts containing different wt% of WD were prepared ($0.1WDSiO_2$, $0.2WDSiO_2$, $0.4WDSiO_2$ and $0.6WDSiO_2$). After impregnation, samples were dried at room temperature in a vacuum-desiccator for 8h.

In all cases the catalysts were characterized by ^{31}P-MAS-NMR in Bruker MSL-300 equipment with a 121.496 MHz frequency; Chemical shifts were expressed in parts per million (ppm) with respect to 85% H_3PO_4 as an external standard. Also their FTIR spectra were determined in Nicolet IR200 equipment on pellets with potassium bromide in the range 400 to 4000 cm^{-1}. The acidity of the catalyst was determined by potentiometric titration using a solution of n-butylamine in acetonitrile in Metrohm 794 Titrino equipment.

General Procedure for the Synthesis of Benzodiazepines

The solid catalyst (1% mmol relative to dione) was added a mixture of 1,3-diphenyl-1,3-propanedione (1 mmol) and the correspondind *o*-phenyldiamine (2 mmol), and then heated to 80ºC with stirring. After completion the mixture was extracted with toluene (2 x 2 mL), treated with anhydrous sodium sulphate and then the solvent was removed in vacuum. The crude reaction product was purified by silicagel column chromnatography using hexane-ethyl acetate as eluent. This gives pure benzodiazepines that were characterized by comparison (thin layer chromatography and physical constants) with standard samples prepared by conventional methods and ^{1}H-NMR and ^{13}C-NMR.

Catalyst Reuse

In order to study the reuse of the catalyst, it was washed with toluene (3 mL) after its filtration from the reaction media, and it dried in vacuum at 80ºC up to constant weight.

RESULTS AND DISCUSSION

Catalyst Characterization

The ^{31}P-MAS-NMR spectrum was carried out and the only resulting signal matches the literature value of -12.6 ppm [23, 24]. FTIR spectra show the typical P-O stretching 1091 cm^{-1}, W-O-W 911 cm^{-1} and 778 cm^{-1}, and W=O 963 cm^{-1}signals. Silica-supported acids exhibits the same bands with a widening due to the loss of symmetry by the silica support. Potentiometric titration shows a maximum acid strength of 827 mV, wich indicates WD acid as strong acid with three different acid sites [24].

^{1}H and ^{13}C-NMR Spectral Data of Products

2,4-Diphenyl -3H-1,5-benzodiazepine (C1)

^{1}H-RMN (DMSO-d6, 400 MHz): δ 3.70 (2H, br s), 7.38 (2H, ddd), 7.45 (6H, m), 7.64 (2H, ddd), 8.00 (4H, m).

^{13}C-RMN (DMSO-d6, 100 MHz): δ 35.06, 125.4, 128.15, 128.72, 128.74, 130.63, 137.32, 140.73, 154.23.

2,4-Diphenyl -3H-6-methyl-1,5-benzodiazepine (C2)

^{1}H-RMN (DMSO-d6, 250 MHz): δ 2.60 (3H, s), 3.70 (2H, br s), 7.27 (2H, m), 7.46 (7H, m), 8.02 (4H, m).

^{13}C-RMN (DMSO-d6, 100 MHz): δ 18.66, 35.01, 125.05, 126.51, 128.05, 128.24, 128.62-128.71, 130.38-130.51, 136.30, 137.43-137.45, 139.06-140.42, 151.75-153.87.

2,4-Diphenyl -3H-7-chloro-1,5-benzodiazepine (C3)

^{1}H-RMN (DMSO-d6, 400 MHz): δ 3.70 (2H, br s), 7.31 (1H, ddd), 7.45 (6H, m), 7.56 (1H, d), 7.63 (1H, d), 7.98 (4H, m).

Table 1. Effect of temperature on 2-(2-hydroxy)-phenyl-4-phenyl-3*H*-1,5-benzodiazepine synthesis.

Entry	Temp. (ºC)	Yield %
1	80	-
2	100	45
3	130	78
4	140	70

Table 2. Effect of reaction time on 2-(2-hydroxy)-phenyl-4-phenyl-3*H*-1,5-benzodiazepine yield.

Entry	Time (min)	Yield (%)
1	15	69
2	30	78
3	45	80
4	60	78

Table 3. Effect of the molar ratio of reactants on 2-(2-hydroxy)-phenyl-4-phenyl-3*H*-1,5-benzodiazepine yield.

Entry	Molar Ratio (Diamine:dione)	Yield %
1	1:1	78
2	1.5:1	80
3	2:1	86
4	3:1	85

^{13}C-RMN (DMSO-d6, 100 MHz): 35.16, 125.78, 128.04, 128.17, 128.23, 128.77, 130.08, 130.46, 130.85-130.97, 136.90, 137.05, 139.29, 141.42, 154.37, 154.94.

2-(2-Hydroxy)-phenyl-4-phenyl-3H-1,5-benzodiazepine (C4)

^{1}H-RMN (DMSO-d_6, 400 MHz): δ 3.80 (2H, br s), 6.90 (1H, t), 7.02 (1H, dd), 7.40 (3H, m), 7.48 (3H, m), 7.58 (1H, dd), 7.66 (1H, dd), 7.82 (1H, dd), 8.06 (2H, m), 14.52 (1H, S).

^{13}C-RMN (DMSO-d_6, 100 MHz): δ 33.41, 117.95, 118.44, 118.56, 125.89, 126.35, 127.95, 128.35, 128.38, 128.83, 129.05, 131.04, 133.59, 136.83, 137.26, 141.66, 155.25, 158.52, 162.56.

The condensation reaction was initially studied using 1-phenyl-3(2-hydroxiphenyl)-1,3-propanedione and *o*-phenyldiamine as substrates. From this point different conditions were checked for the reaction, such as temperature, time or catalyst amount.

The influence of temperature on the production of benzodiazepines is shown in Table **1**. Four experiments were performed working under solvent-free conditions and 30 min reaction time at different temperatures.

The results show better yields at higher temperatures. The test performed at 80ºC gives no product, even after 2 h. At 100ºC the reaction gives a low 45% yield, and the optimal temperature value is 130ºC with a yield of 78%. Results obtained at 140ºC show that a temperature higher than 130ºC does not improve the yields.

The reaction time was also tested at the selected optimal temperature of 130ºC, using four different times of 15, 30, 45 y 60 min (Table **2**). A good yield is obtained at 15 min of reaction, reaching the optimal yield at 30 min, without any variation at longer reaction times like 45 or 60 min.

Another key factor in these tests is the molar ratio of reactants. Table **3** shows the results on different proportions of the compounds using the previously defined optimal temperature (130ºC) and time (30 min): equimolar quatities gives a good yield, but an excess of *o*-phenyldiamine improves the yield with a ratio 2:1 of *o*-phenyldiamine / 1-phenyl-3-(2-hydroxyphenyl)-1,3-propanedione giving the best performance.

Taking the molar ratio 2:1 as optimal condition, under solvent-free conditions at 130ºC and 30 min. of reaction time, various amounts of the bulk catalyst were tested. The results are listed in Table **4**. It can be seen that 20 mg of Wells-Dawson (0.5 % mmol relative to dione) acid gives the best yield, and no additional amount of catalyst is required to improve it. Also, it can be seen that a lesser molar proportion of bulk WD acid gives lower yields.

Table 4. Effect of catalyst ammount on 2-(2-hydroxy)-phenyl-4-phenyl-3*H*-1,5-benzodiazepine yield.

Entry	Catalyst Ammount (mg)	Catalyst Ammount (mmol %)	Yield (%)
1	10	0.25	49
2	20	0.5	86
3	30	0.75	86
4	40	1	85

To study the reusability of the catalyst in the same reaction, the recovered catalyst was reused in the same conditions and proportions (130ºC, under solver free conditions, with 0.5% mmol of catalyst and 2:1 diamine:dione molar ratio), over three consecutive tests. To make this possible the used catalyst was filtered and then washed with toluene and dried in vacuum. The results, which are given in Table **5**, suggest no appreciable variations when the catalyst is reused four consecutive times.

Another test was applied to the catalyst to determine the effect of the different supported $WDSiO_2$ acids prepared in identical conditions, preserving the optimal %mmol proportion of WD. The results are listed in Table **6**.

It can be observed that $0.2WDSiO_2$ and $0.4WDSiO_2$ giver similar yields in identical conditions, with the bulk catalyst showing the best performance. A higher proportion of WD

Table 5. Effect of catalyst reuse on 2-(2-hydroxy)-phenyl-4-phenyl-3*H*-1,5-benzodiazepine yield.

Entry	Cycle	Yield %
1	0	86
2	1	84
3	2	83
4	3	83

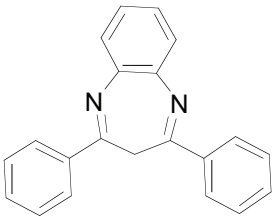
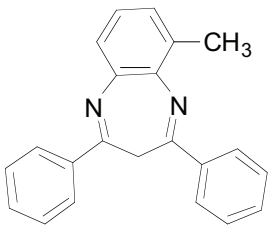
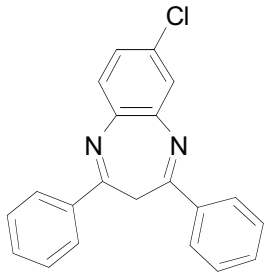
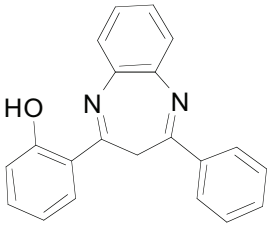
Table 6. Effect of catalyst support on 2-(2-hydroxy)-phenyl-4-phenyl-3*H*-1,5-benzodiazepine yield (%).

Entry	Catalyst	Yield (%)
1	0.1WDSiO$_2$	55
2	0.2WDSiO$_2$	76
3	0.4WDSiO$_2$	79
4	0.6WDSiO$_2$	71

(0.6WDSiO$_2$) reduces the yields, and lesser quantities (0.1 WDSiO$_2$) also give poor results. Based on all the results presented in Tables **1**-**6**, bulk Wells-Dawson heteropolyacid is the more effective catalyst for the reaction.

Base on these results, and using the optimal reaction conditions previously defined (2 mmol of *o*-phenyldiamine and 1 mmol of 1-phenyl-3-(2-hydroxyphenyl)-1,3-propanedione at 130ºC under solvent free conditions, over a 30 min reaction time in the presence of 0.5% mmol of WD bulk acid as catalyst) different benzodiazepines were synthesized. Results shown in Table **7**, give very good yields on benzodiazepine formation with lesser results in non-susbtituted benzodiazepine, and resulting the best yield for the methyl-substituted benzodiazepine.

Table 7. Synthesis of different substituted 3*H*-1,5-benzodizepines.

Product	Product	Yield (%)
C1		56
C2		88
C3		81
C4		78

CONCLUSION

In conclusion, we have developed a mild, efficient and environmentally friendly protocol for the selective synthesis of benzodiazepines from 1-phenyl-3(2-hydroxiphenyl)-1,3-propanedione and a *o*-phenyldiamine in the presense of the Wells-Dawson type $H_6P_2W_{18}O_{62}.24H_2O$ acid, a heteropolyacid capable of being recovered and reused without loss of activity in this reaction. In this way we report an environmentally benign methodology for the preparation of compounds of pharmaceutical and agricultural interest whose major advantages are solvent-free conditions and the use of a recoverable solid heteropolyacid.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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