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Phosphotungstic acid($H_3PW_{12}O_{40}$) catalyzed highly efficient synthesis of benzodiazepines under solvent-free conditions

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ABSTRACT

An efficient and clean synthesis of benzodiazepines is described by the reaction of *o*-phenylenediamine with different types of methyl/methylene ketones in the presence of catalytic amounts of Phosphotungstic acid ($H_3PW_{12}O_{40}$) under solvent-free conditions at room temperature in excellent yields.

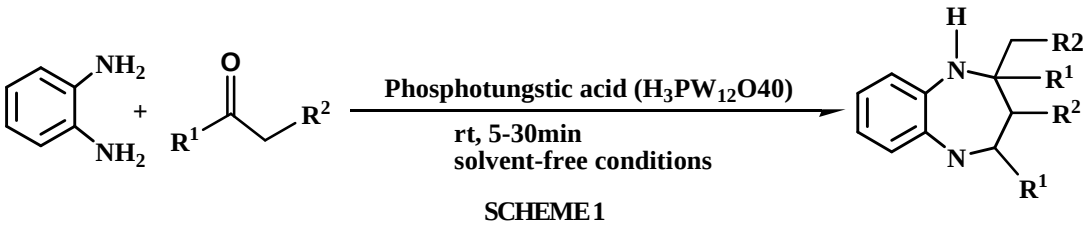
KEYWORDS

$H_3PW_{12}O_{40}$;
o-Phenylenediamine;
Methyl/methylene ketones;
Solvent-free conditions.

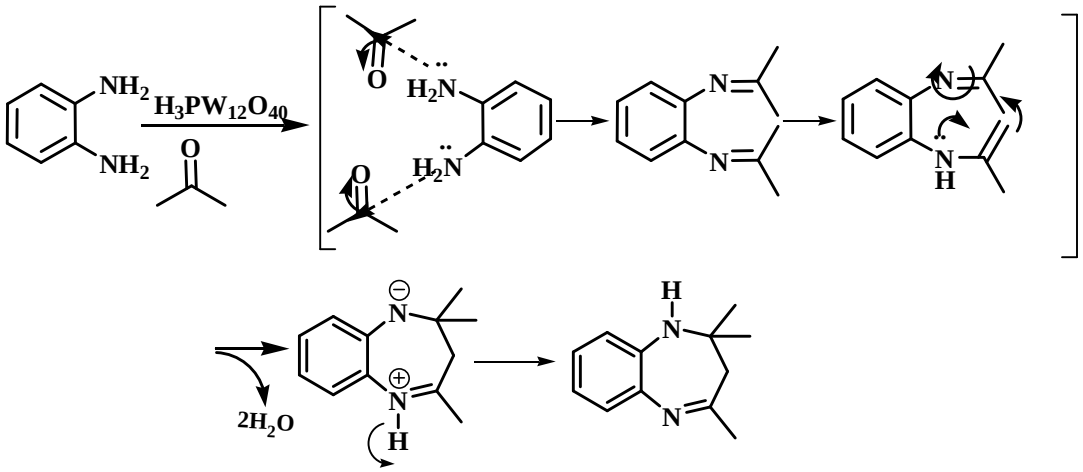
INTRODUCTION

The increasing demand of clean and efficient chemical reactions had led to the development of solvent-free synthesis, which is of great current interest. On the other hand, organic reactions using reusable and water tolerant catalyst also received much attention in recent years. They can conveniently be handled and removed from the reaction mixture, making the experimental procedure simple and eco-friendly. Therefore organic reactions using simple and efficient catalyst will be an ideal methodology, if the catalyst shows high catalytic activity, under solvent-free conditions[1].

The synthesis of benzodiazepines is of interest, as they possess a large number of pharmacological properties[2] such as anticonvulsant, anti-anxiety, analgesic, hypnotic, sedative, antidepressant and anti-inflamatory agents. The benzodiazepines are also used as valuable precursors in the synthesis of various fused heterocyclic systems[3] such as triazolo-, oxazino-, oxadiazolo- and furano-benzodiazepines. In addition to this they also find commercial use as dyes for acrylic fibers[4]. Despite their importance from the pharmacological, industrial and synthetic point of view, comparatively few methods for the preparation of benzodiazepines have been reported. These include condensation reaction of o-phenylenediamine with α, β unsaturated carbonyl compounds in the presence of a base[5], with β-halo ketones[6] or with ketones having α-hydrogen(s) in the presence of lewis acid catalysts such as $Yb(OTf)_3$[7], $InBr_3$[8], BF_3-etherate[9], SiO_2[10], MgO and $POCl_3$[11], silica supported fluoroboric acid[12], I_2[13], $Me_2S^+BrBr^-$[14], $Sc(OTf)_3$[15] and $AgNO_3$[16] etc. However, all these methods involve one or other limitations such as long reaction times and tedious work up procedures with unsatisfactory yields. An efficient synthesis of benzodiazepines is highly desirable. In view of current interest in catalytic processes, there is merit in developing synthesis of benzodiazepines using inexpensive, mild and non-polluting reagents.



SCHEME 1



SCHEME 2: Proposed Mechanism

In recent decades, the use of heteropoly acids (HPAs) as catalysts for fine organic synthetic processes have been developed and are important for industries related with fine chemicals[17], including flavors, pharmaceuticals and food industries[18]. Heteropoly acids are more active catalysts than conventional inorganic and organic acids for various reactions in solutions[19]. They are used as industrial catalysts for several liquid phase reactions[20-23]. Among heteropoly acids, polytungstic acids are the most widely used catalysts owing to their high acid strengths, thermal stabilities, and low reducibilities. Catalysts based on heteropoly acids as Bronsted acids have many advantages over liquid acid catalysts. They are non-corrosive and environmentally benign, presenting fewer disposal problems. Solid heteropoly acids have attracted much attention in organic synthesis owing to easy work-up procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of the catalysts[24]. Supported heteropoly acid on silica gel has been used as effective catalyst for Diels Alder[25a] and Fries rearrangement[25b], Friedel Crafts reactions[25c,d]. In the last few years, have been reported new catalytic activities of $H_3PW_{12}O_{40}$[26], and its salts[27], have been reported for basic chemical transformations such as an effective catalyst for protection of carbonyl groups as their acetals[27], tetrahydropyranylation of alcohols[28], dihydropyrimidinones[29], and more recently a direct synthesis of N-methyl benzimidazoles have been reported using $H_3PW_{12}O_{40}$ as an efficient catalyst[30].

In this report (SCHEME 1) we describe an efficient method for the synthesis of benzodiazepines. This method does not need expensive reagents or special care to exclude the moisture from the reaction medium(solvent-free conditions). Initially, *o*-phenylenediamine (1mmol) was reacted with acetone (2.2mmol) using of $H_3PW_{12}O_{40}$ (0.05equiv.) at room temperature under solvent-free conditions to give the corresponding benzodiazepines in 98% yield in very short time. Whereas, in the absence of the catalyst the reaction does not yield the desired product even after 24 h stirring at room temperature. In order to check the catalytic activity of $H_3PW_{12}O_{40}$, we compared with various other Lewis acid catalysts. However, $H_3PW_{12}O_{40}$ was found to be most effective in terms of reaction time as well as yield of the product(TABLE 1). Increasing the amount of $H_3PW_{12}O_{40}$ (0.05 equiv. to 1 equiv.) did not show significant influence on the rate of the reaction as

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TABLE 1: Comparison of the catalytic activity of $H_3PW_{12}O_{40}$ with other catalysts on the reaction of *o*-phenylenediamine and acetone under solvent-free conditions at room temperature

Entry	Catalyst(0.05equiv.)	Time(min)	Yield (%)
1	$Yb(OTf)_3$	30	96
2	$InBr_3$	30	96
3	SiO_2	180	94
4	HBF_4-SiO_2	30	96
5	I_2	10	95
6	$Me_2S^+BrBr^-$	60	96
7	$Sc(OTf)_3$	180	96
8	$AgNO_3$	30	99
9	$LiClO_4$	30	90
10	$FeCl_3$	30	90
11	None	24h	No product
12	$H_3PW_{12}O_{40}$	5	98

well as yield(TABLE 2), suggesting regeneration of catalyst in the reaction medium(SCHEME 2). Using 0.05 equiv. of $H_3PW_{12}O_{40}$ under solvent-free conditions gave good to excellent yields(>98%) of the corresponding benzodiazepines. Encouraged by the success of this reaction, using catalytic amount of $H_3PW_{12}O_{40}$, various α-hydrogen(s) containing ketones were reacted with differently substituted *o*-phenylenediamine to afford corresponding benzodiazepines in excellent yields (SCHEME 1, TABLE 3). Further, both primary and secondary ketones having α-hydrogens such as methyl ethyl ketone and methyl *iso*-butyl ketone were reacted. Only less sterically hindered primary carbon having α-hydrogen involved in the cyclization reaction to give the products.

In conclusion the present procedure for the synthesis of benzodiazepines in presence of catalytic amount of $H_3PW_{12}O_{40}$ has the advantage of mild reaction conditions, inexpensive catalyst with high yields of products, simple experimental work-up procedure and no organic solvent or inert atmosphere as reaction medium, which makes it is a useful and important addition to the present existing methods.

TABLE 2 : Optimization of reaction conditions on the reaction of *o*-phenylenediamine and acetone using $H_3PW_{12}O_{40}$

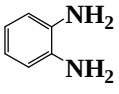
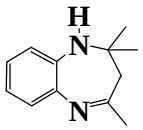
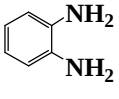
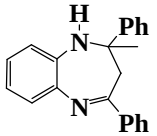
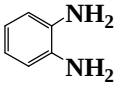
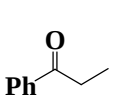
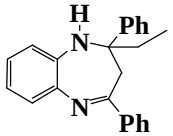
Entry	Solvent	$H_3PW_{12}O_{40}$	Time (min)	(%) Yield
1	DCM	1.0	180	90
2	THF	1.0	180	75
3	CH_3CN	1.0	180	70
4	$CHCl_3$	1.0	180	89
5	Acetone	1.0	30	95
6	Neat	1.0	4	97
7	Neat	0.5	5	98
8	Neat	0.25	5	98
9	Neat	0.1	5	98
10	Neat	0.05	5	98

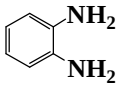
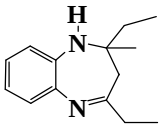
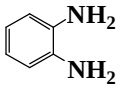
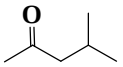
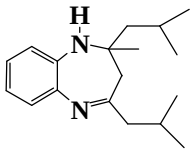
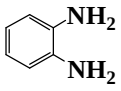
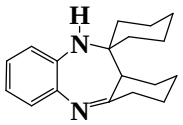
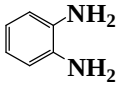
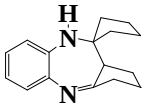
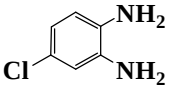
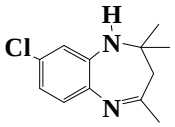
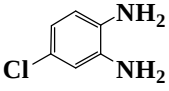
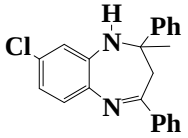
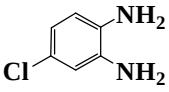
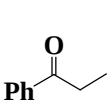
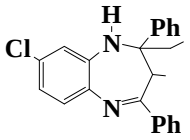
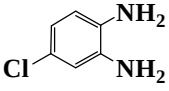
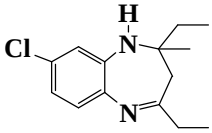
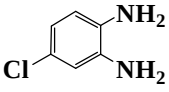
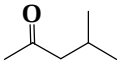
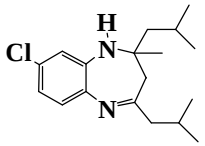
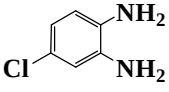
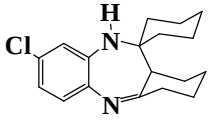
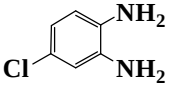
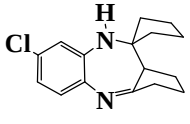
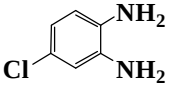
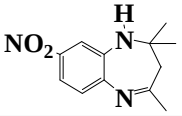
Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on Merck plates and spotting was done using iodine or uv-light. ^1H NMR on VARIAN 200 and GEMINI 300MHz instrument and Mass spectra were recorded on agilent-LC-MS instrument giving only $M^{+\cdot}$ Values using Q+1 mode. Substituted o-phenyldiamine, different substituted Ketones and Acid Catalysts were obtained from the commercial supplier Lobachem India.

EXPERIMENTAL

To a mixture of o-phenylenediamine(1mmol) and ketone(2.2mmol) was added $H_3PW_{12}O_{40}$(0.05equiv.). The reaction was stirred at room temperature under

TABLE 3 : Synthesis of benzodiazepines in the presence of Phosphotungstic acid ($H_3PW_{12}O_{40}$) under solvent-free conditions

Entry	Diamine	Ketone	Producta	Time(min)	Yield (%)b
1				5	98
2				15	95
3				20	95

Entry	Diamine	Ketone	Producta	Time(min)	Yield (%)b
4				10	95
5				20	90
6				30	90
7				25	96
8				5	96
9				10	95
10				25	90
11				15	97
12				15	95
13				30	90
14				20	90
15				5	98

[a]All the compounds were characterized by [1]H NMR and mass spectral data. [b]Isolated yields after column chromatography

solvent-free conditions for an appropriate time (TABLE 3). After completion of the reaction as monitored by TLC, water(10mL) was added to the reaction mixture and the product was extracted into ethyl acetate

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(3×20mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated in vacuum to give crude mass, which was purified over silica gel column chromatography using (1:9) ethyl acetate and hexane as eluent to afford corresponding product in good yields Entry **1**. ^{1}H NMR (300MHz, $CDCl_3$) δ1.35(s, 6H, $2CH_3$), 2.25(s, 2H, CH_2), 2.35(s, 3H, CH_3), 2.90(br, s, 1H, NH), 6.20-6.30(d, 1H, J=8.23Hz, Ar-H), 6.90-7.00(m, 2H, J=3.23Hz, Ar-H), 7.15(d, 1H, J=8.23Hz, Ar-H); EIMS: m/z 188. Entry **2**. ^{1}H NMR(300 MHz, $CDCl_3$) δ1.81(s, 3H, CH_3), 2.93(d, 1H, J=12.8Hz, CH^a), 3.12(d, 1H, J=12.8Hz, CH^b), 3.45(br, s, 1H, NH), 6.80(d, 1H, J=8.23Hz, Ar-H), 6.90-7.00(m, 2H, J=3.23Hz, Ar-H), 7.30(m, 6H, J=8.23Hz, Ar-H), 7.55-7.65(m, 5H, J=8.23Hz, Ar-H); EIMS: m/z 312. Entry **4**. ^{1}H NMR(300MHz, $CDCl_3$) δ0.90(t, 3H, J= 3.50Hz), 1.25(m, 6H), 1.50-1.70(m, 2H), 2.20(q, 2H, J=3.50Hz), 2.50-2.68(q, 2H, J=3.23Hz), 3.60(s, br, 1H), 6.65(m, 1H), 6.95-7.00(m, 2H), 7.10(m, 1H); EIMS: m/z 216. Entry **5**. ^{1}H NMR(300 MHz, $CDCl_3$) δ1.00(m, 12H, $4CH_3$), 1.25(m, 2H, 2CH), 1.30(s, 3H, CH_3), 1.75(m, 2H, CH_2), 2.20-2.30(m, 2H, CH_2), 2.40(d, 2H, CH_2), 6.60(m, 1H, Ar-H), 6.90(m, 2H, Ar-H), 7.10(m, 1H, Ar-H); EIMS: m/z 272. Entry **6**. ^{1}H NMR(300 MHz, $CDCl_3$) δ1.96-2.10(m, 14H, $7CH_2$), 2.90-3.20(m, 3H, CH, CH_2), 5.00(br, s, 1H, NH), 6.70(m, 1H, Ar-CH), 7.10(m, 2H, Ar-CH), 7.20-7.50(m, 1H, Ar-CH); EIMS: m/z 268. Entry **7**. ^{1}H NMR(300MHz, $CDCl_3$) 1.90-2.09(m, 12H, $6CH_2$), 2.95-3.30(m, 3H, CH, CH_2), 4.50(br, s, 1H, NH), 6.60(m, 1H, Ar-H), 7.15-7.20(m, 2H, Ar-H), 7.25-7.35(m, 1H, Ar-H); EIMS: m/z 240. Entry **8**. ^{1}H NMR(300 MHz, $CDCl_3$) δ1.27(m, 6H, $2CH_3$), 2.22(s, 2H, CH_2), 2.25(s, 3H, CH_3), 6.59(s, 1H, Ar-H), 6.85(s, 1H, Ar-H), 7.00(s, 1H, Ar-H); EIMS: m/z 222.

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