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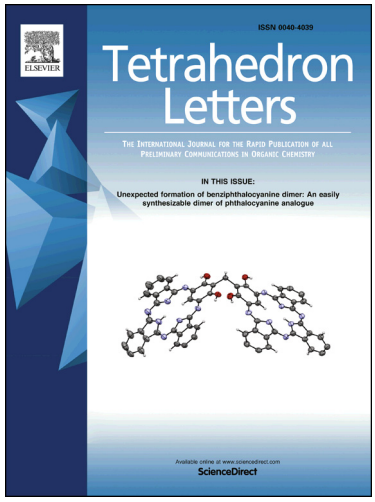

An efficient, environmentally benign, and solvent-free protocol for the synthesis of 4-substituted 1,5- benzodiazepines catalyzed by reusable sulfated polyborate

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Graphical Abstract

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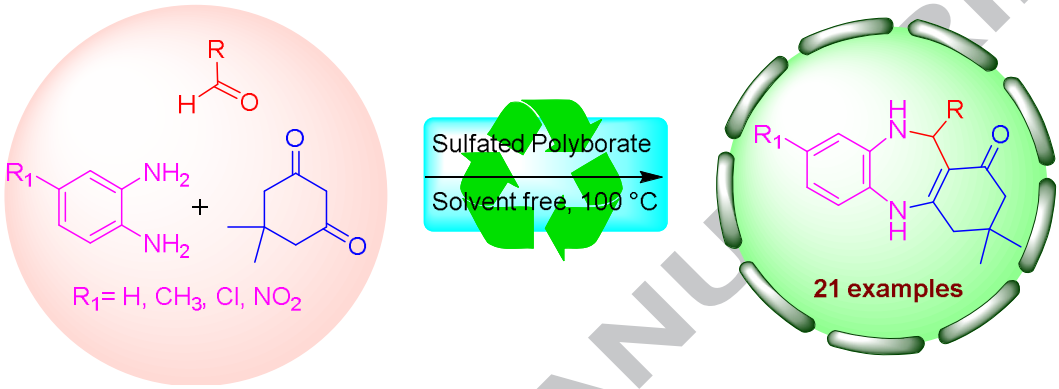

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ABSTRACT

An efficient and environmentally benign method has been developed for the one-pot solvent-free synthesis of 4-substituted-1,5-benzodiazepines *via* three-component reaction of *o*-phenylenediamine, dimedone with a variety of aldehydes catalyzed by sulfated polyborate under solvent-free condition. The major advantages of the present method are good to excellent yields, shorter reaction time, simple experimental procedure, easy workup procedure, solvent-free reaction conditions, recyclability of the catalyst and ability to tolerate a variety of functional groups which gives economical as well as ecological rewards.

Recently, the development of a simple, highly elegant, and eco-friendly synthetic method for widely used organic compounds from readily available catalyst or reagents is one of the major challenges for chemists [1]. Multicomponent reactions have emerged as a powerful tool in generating products in medicinal chemistry as well as organic synthesis because they trigger the conversion of three or more starting components in one pot to a highly functionalized product showing maximum molecular diversity, complexity, and selectivity. Therefore, these reactions are eco-friendly, highly atom economical, and synthetically efficient in terms of reduced time, steps, energy, and the consumption of chemicals as well as solvents [2-6]. *N*-heterocyclic compounds represent one of the most valuable building blocks for biologically active molecules, drugs and intermediates.[7]

Benzodiazepines are the important heterocyclic compounds, acquired considerable attention in medicinal chemistry due to their widespread biological and pharmacological activities.[8,9] (Fig. 1). Its remarkable central nervous system (CNS) depressant activity[10] made them one of the most widely prescribed classes of psychotropics.[11,12] Some important examples are diazepam and chlordiazepoxide that act as anti-anxiety drugs[8] and clozapine from the piperidinyl dibenzodiazepine in schizophrenia drugs, as well as apafant act as the platelet-activating factor inhibitor and pirenzepine act as the muscarinic receptor-M1 antagonist.[13] They are also used as dyes for acrylic fibres[14] in photography. Modifications in these heterocycles have been made and the anxiolytic effect of benzodiazepines (clobazam) has been described. Benzodiazepine compounds are extensively sold as psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity. In addition, 1,5-benzodiazepines are used

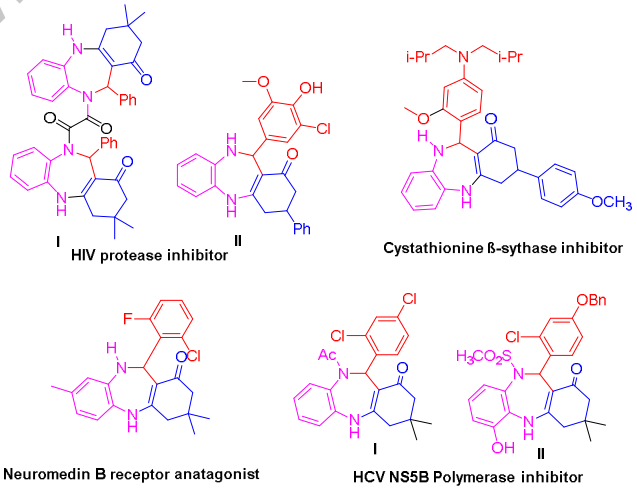

Fig.1. Pharmacological active compounds

as synthons for the preparation of other fused ring systems such as oxadiazolo-, triazolo-, oxazino- or furanobenzodiazepines.[15-17]

The 1,5-dibenzodiazepines have been reported to exhibit inhibitory activities towards HIV-1 protease[18,19] and hepatitis C virus (HCV) NS5B[20] as well as finding several applications in medicinal chemistry,[21] where they have been used as hypnotic,[22] anti-inflammatory,[23] anticoagulant,[24] antibacterial,[25] antiepileptic,[26,27] antidepressant,[28] and analgesic agents.[29]

Due to the versatile applicability highlights the importance of accessing efficient synthetic routes to well-designed 4-substituted-1,5-benzodiazepines. A number of methods have been developed for the synthesis of 4-substituted-1,5-benzodiazepines. It has been carried out by three-component condensation of *o*-phenylenediamine, dimedone and

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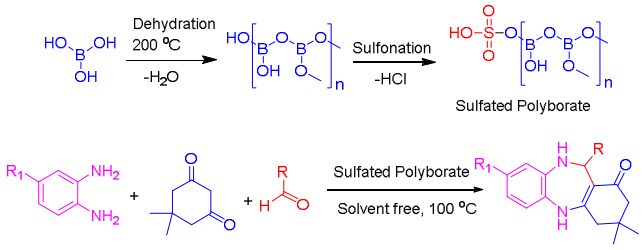


Scheme 1. Schematic representation of sulfated polyborate catalyzed synthesis of 4-substituted-1,5-benzodiazepines.

aldehyde variants under various conditions such as oxalic acid in water,[30] acetic acid in ethanol under reflux,[8] acetic acid in toluene, [31] HCl in ethanol,[32] and H_2SO_4 in ethanol.[33] In addition, they have been synthesized by the condensation of 2-formyl benzoic acid, *o*-phenylenediamine and tetronic acid in water under microwave irradiation as a hetero-Cope rearrangement,[34] cycloaddition reaction of 2,2-dihydroxy-1-phenylethanone, *o*-phenylenediamine, and dimedone derivatives.[35]

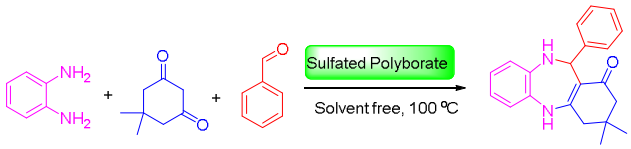
Recently, some strategies have been introduced for the synthesis of 4-substituted benzodiazepines in the presence of a wide variety of catalysts such as Cu/GA/Fe_3O_4@SiO_2 NCPs,[36] *N*-methyl-2-pyrrolidonium hydrogen sulfate as an ionic liquid,[37] zinc sulfide nanoparticles *via* grinding method,[38] graphene oxide nanosheets,[39] ZnS nanoparticles,[13] ZrO_2-Al_2O_3,[40] chitosan-supported superparamagnetic iron oxide nanocomposite,[41] DES (choline chloride:urea),[42] and promoted by microwaves.[43]

Each of these methods has their own advantages but may suffer from one or more shortcomings such as long reaction time, multi-step sequences or need anhydrous conditions, poor yields, laborious workup, use of organic solvents, difficult recovery and reusability of the catalysts, and the use of hazardous as well as excess of catalysts or reagent. Hence, the development of clean, efficient, environmentally benign, and high yielding rapid reaction procedure using cost-effective and recyclable catalyst is very much desirable.

In the perpetuation of the development of eco-friendly, convenient, and practical catalytic methods for the current interest in organic synthesis and commercial process; recently we have synthesized, characterized sulfated polyborate and proved its efficiency for various useful organic transformations.[44-56] Its easy preparation, mild acidity, eco-friendliness, and reusability have encouraged us to investigate its potential to catalyze many other useful organic transformations. Therefore, inspired by our previous finding, herein we report a rapid, efficient, and green method for synthesis of 4-substituted-1,5-benzodiazepines *via* one-pot, solvent-free condensation of a variety of aldehydes with *o*-phenylenediamine and dimedone in the presence of a sulfated polyborate as a recyclable catalyst under solvent-free conditions (Scheme 1). This reaction provided facile access to the target molecules in high yields over short reaction times using sulfated polyborate as a catalyst. Furthermore, this method is environmentally benign and robust and involves easy product separation and workup procedures.

A literature search revealed that boric acid catalyzes many useful organic transformations above 100 °C.[57,58] Boric acid dehydrates above 100 °C and turns to its polymeric forms, which could be the active species catalyzing the reaction.[59] Dehydrative polymerization of boric acid liberates water molecules which may hamper the progress of the reaction.

This persuades us to develop a polymeric boric acid catalyst with mild Bronsted acidity. To accomplish this boric acid was dehydrated at 200 °C to convert it into its polymeric Lewis acid form and then sulfonated to introduce the mild Bronsted acid



Scheme 2. Synthesis of 3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one

Table 1

Effect of catalyst loading and temperature for the synthesis of 3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one [a]

Entry	Catalyst (wt %)	Temperature (°C)	Time (min)	Yield[b] (%)
1	-	100	180	NR[c]
2	2.5	100	90	72
3	5	100	30	80
4	7.5	100	15	89
5	10	100	10	95
6	15	100	10	95
7	10	r.t.	60	NR[c]
8	10	60	60	30
9	10	80	60	74
10	10	120	10	95

[a] Reaction conditions: *o*-phenylenediamine (1 mmol), dimedone (1mmol), benzaldehyde (1 mmol) [b] Isolated yield. [c]No reaction

Table 2

The effect of the solvents on the synthesis of 3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one [a]

Entry	Solvent	Temperature (°C)	Time (min)	Yield[b] (%)
1	Solvent-free	100	10	95
2	Water	Reflux	60	traces
3	MeCN	Reflux	60	25
4	THF	Reflux	60	32
5	EtOH	Reflux	60	70
6	Toluene	Reflux	60	43
7	DMF	100	60	55
8	DMSO	100	60	58

[a] Reaction conditions: *o*-phenylenediamine (1 mmol), dimedone (1mmol), benzaldehyde (1 mmol), sulfated polyborate 10 wt % [b] Isolated yield.

character. Boron being an electron deficient element and electron-withdrawing effect of adjacent sulfate enhances its Lewis acidity; hence sulfated polyborate has both Lewis as well as Bronsted acid characters (Scheme 1).

For initial screening, the study was designed for the synthesis of 4-substituted-1,5-benzodiazepines to investigate the suitability of sulfated polyborate as a catalyst at different reaction conditions. In the initial experiment, an equimolar mixture of *o*-phenylenediamine, dimedone, and benzaldehyde a representative substrate was used (Scheme 2). The results are summarized in Table 1

Table 3

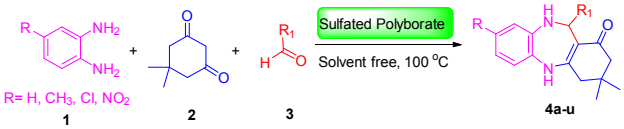
Results of the conditional experiments to ascertain role of sulfated polyborate.

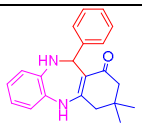
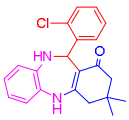
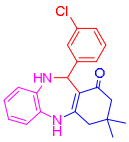
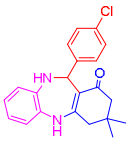
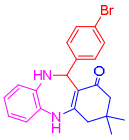
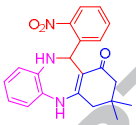
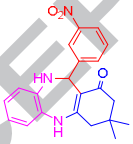
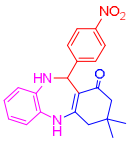
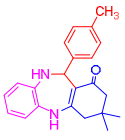
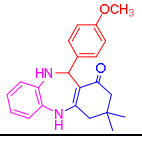
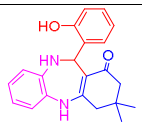
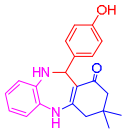
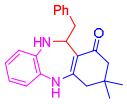
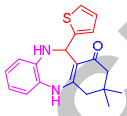
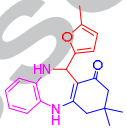
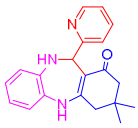
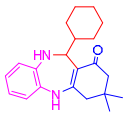
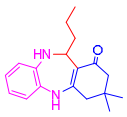
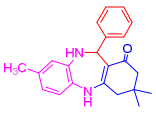
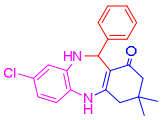
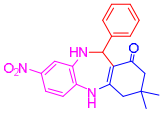
Entry	Catalyst	Condition	Time (min)	Yield[b] (%)
1.	Sulfated polyborate	Neat/100 °C	10	95
2.	Polyboric acid	Neat/100 °C	300	NR[c]
3.	Boric acid	Neat/100 °C	300	NR[c]
4.	HCl	EtOH/reflux	300	NR[c]
5.	H_2SO_4	EtOH/reflux	300	NR[c]

[a] Reaction conditions: *o*-phenylenediamine (1 mmol), dimedone (1mmol), benzaldehyde (1 mmol) [b] Isolated yield. [c]No reaction

Table 4

Sulfated polyborate catalyzed synthesis of 4-substituted 1,5-benzodiazepines [a, 60]



Entry	Aldehyde (R_1)	Product	Time (Min)	Yield (%)
1	C_6H_5		10	95
2.	2-Cl-C_6H_4		12	90
3.	3-Cl-C_6H_4		10	93
4.	4-Cl-C_6H_4		10	95
5.	4-Br-C_6H_4		10	93
6.	2- O_2N-C_6H_4		10	95
7.	3-O_2N-C_6H_4		10	96
8.	4-O_2N-C_6H_4		10	98
9.	4-CH_3-C_6H_4		12	92
10.	4-CH_3O-C_6H_4		12	90
11.	2-HO-C_6H_4		15	88
12.	4-HO-C_6H_4		12	90
13.	$C_6H_5CH_2$		12	91
14.	2-Thienyl		15	88
15.	5-Methyl furan-2-yl		15	86
16.	2-Pyridyl		15	85
17.	*c*-C_6H_{11}		15	86
18.	*n*-C_3H_7		15	83
19.	C_6H_5		10	93
20.	C_6H_5		10	95
21.	C_6H_5		10	94

[a] Reaction conditions: *o*-phenylenediamine (1 mmol), dimedone (1mmol), aldehyde (1 mmol), sulfated polyborate 10 wt % [b] Isolated yield.

The amount of catalyst and temperature mainly affect the efficiency of the reaction. To understand the effect of the catalyst loading on time and yields of the product (Table 1, entries 1-6), a control experiment was performed in the absence of a catalyst at 100 °C but the reaction does not proceed. (Table 1, entry 1). Further experiments were conducted to optimize the amount of sulfated polyborate catalyst and an increase in the catalyst loading increased the product yield with a significant reduction in the reaction time was observed (Table 1, entries 2-

5). The catalyst loading beyond 10 wt % was not advantageous (Table 1, entries 5 and 6). Hence, 10 wt % catalyst loading was chosen for further study. (Table 1, entry 5).

Temperature played a vital role in the synthesis of 4-substituted-1,5-benzodiazepines (Table 1, entries 7-10). The temperature effect was assessed at ambient, 60, 80, 100 and 120 °C in presence of sulfated polyborate. The reaction did not proceed at room temperature (Table 1, entry 7) while proceeded at 60 and 80 °C but took longer reaction time with a poor yield (Table 1, entries 8 and 9). The reaction proceeds at 100 °C with increased product yield in shorter reaction time (Table 1, entry 5). The reaction temperature beyond 100 °C was not advantageous (Table 1, entry 9). Therefore, 100 °C was chosen as optimum temperature.

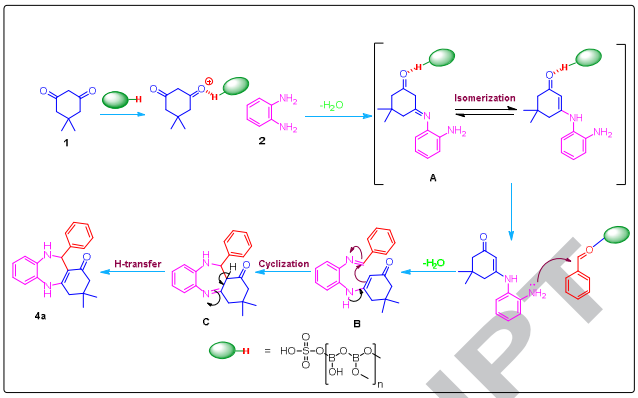
The effect of various solvents on time and yield of the reaction was ascertained (Table 2, entries 1-8). None of the solvents should the advantage of time and yield over solvent-free condition. Hence, the solvent-free condition was regarded as best for the cost and environmental benefits. In all the experiments, the products were isolated by aqueous quenching followed by filtration and recrystallized from methanol. To understand the role of the sulfated polyborate for the synthesis of 4-substituted 1,5-benzodiazepines, conditional experiments were carried out separately with boric acid, polyboric acid, as well as with ethanolic H_2SO_4, and HCl. The results substantiate the catalytic role of sulfated polyborate over other acids (Table 3).

To study the synthetic utility and scope, optimized reaction condition[60] was applied to various aldehydes and substituted *o*-phenylenediamine. All the substituted aromatic, heterocyclic, alicyclic and aliphatic aldehydes, as well as substituted *o*-phenylenediamine with dimedone, reacted well to afford good to excellent yields of the corresponding 4-substituted-1,5-benzodiazepines in shorter reaction time (Table 4, entries 1–21). To judge the substituent effect on reaction time and yields, aromatic aldehydes bearing various electron-donating or electron-withdrawing functional groups at the *ortho*, *meta* and *para* positions were tested. The nature of substitutions on aromatic aldehydes has no significant effect on the reaction time and yields (Table 4, entries 1–12) except *ortho*-hydroxy benzaldehyde (Table 4, entry 11). This protocol was also extended to heterocyclic, alicyclic and aliphatic aldehydes, resulted in corresponding 4-substituted-1,5-benzodiazepines in good yields but took slightly longer time compared to others (Table 4, entries 13–18). Further, the optimized reaction protocol was also extendable to substituted *o*-phenylenediamine (Table 4, entries 19–21), resulted in good yields of the corresponding 4,7-disubstituted-1,5-benzodiazepines.

Recyclability of the catalyst is an important attribute for the industrial suitability. Therefore, reusability of the catalyst in the model reaction of *o*-phenylenediamine, dimedone, and benzaldehyde under optimized reaction condition was evaluated. In this study, after completion of each reaction cycle, the reaction mixture was quenched with water, and the product was filtered off. The catalyst dissolves in water which was recovered quantitatively by evaporation in a rotary evaporator. The recovered catalyst was recycled for four times with no significant loss in a catalytic activity (Table 5).

Based on the results of the current study, we propose a mechanism for the formation of 4-substituted-1,5-benzodiazepine from *o*-phenylenediamine, dimedone, and benzaldehyde in the presence of sulfated polyborate (Scheme 3).

The proposed mechanism is based on sequential Michael addition and Knoevenagel cyclization reactions. One of the carbonyl group of dimedone (**1**) would undergo an initial Michael addition reaction with *o*-phenylenediamine (**2**) to provide enamine intermediate (**A**).



Scheme 3. Proposed reaction mechanism for the sulfated polyborate catalyzed formation of 4-substituted-1,5-benzodiazepine.

The enamine intermediate then reacts with the aromatic aldehyde (**3**) to give the corresponding diimine **B**, which would undergo an intramolecular dehydrative cyclization to give 4-substituted-1,5-benzodiazepines (**4a**) via intermediate (**C**) after intramolecular 1,3-proton transfer.

Table 5.
Recyclability of the catalyst[a]

Entry	Number of Cycle	Time (min)	Yield[b] (%)
1	Fresh	10	95
2	1	10	94
3	2	10	92
4	3	10	91
5	4	10	91

[a] Reaction conditions: *o*-phenylenediamine (1 mmol), dimedone (1mmol), benzaldehyde (1 mmol), sulfated polyborate 10 wt % solvent-free, 100 °C.
[b] Isolated yield.

Conclusion

In summary, we have developed a rapid, simple, efficient, and environmentally benign one-pot, a three-component protocol for the synthesis of 4-substituted-1,5-benzodiazepines in the presence of reusable sulfated polyborate as a mild, efficient, eco-friendly, and inexpensive catalyst. Excellent yields, simple experimental procedure, easy workup procedure, shorter reaction time, solvent-free condition, non-hazardous and environment-friendly reaction condition are the key features of this procedure. Moreover, this protocol has the ability to tolerate a wide variety of substituents.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/00.0000/

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60. *General procedure for the synthesis of 4-substituted-1,5-benzodiazepines (**4a**–**u**):*
A mixture of dimedone (1 mmol), *o*-phenylenediamine (1 mmol), aldehyde (1 mmol) and sulfated polyborate (10 wt %) was heated at 100 °C in an oil bath. The progress of the reactions was monitored by TLC. After completion of the reaction, the mixtures were cooled to room temperature and quenched in water; solid precipitated was filtered at vacuum pump, washed with water (3 X 5 mL), dried under vacuum and recrystallization from methanol to afford the pure product for spectral analysis.

Highlights:

- Rapid, efficient, solvent-free and environmentally benign synthesis of 1,5-benzodiazepines.
- Key advantages are high yields, short reaction time and simple work-up procedure.
- Protocol tolerates a variety of aromatic, aliphatic, benzylic, and heterocyclic aldehydes.
- Recyclable catalyst with no significant loss in activity.