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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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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. The major advantages of the present method are good to excellent yields, shorter reaction time, simple experimental procedure, easy workup, solvent-free reaction condition, 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 methods 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] and in photography. Modifications in these heterocycles have been made and the anxiolytic effect of benzodiazepines (clobazam) has been described. Benzodiazepines are extensively sold as psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity. In addition, 1,5-benzodiazepines are used as synthons for the preparation of other fused ring systems such as oxadiazolo-, triazolo-, oxazino- or furanobenzodiazepines.[14–16]

The 1,5-dibenzodiazepines have been reported to exhibit inhibitory activities towards HIV-1 protease[17,18] and hepatitis C virus (HCV) NS5B[19] as well as finding several applications in medicinal chemistry,[20] where they have been used as hypnotic,[21] anti-inflammatory,[22] anticoagulant,[23] antibacterial,[24] antiepileptic,[25,26] antidepressant,[27] and analgesic agents.[28]

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 aldehyde variants under various conditions such as oxalic acid in water,[29] acetic acid in ethanol under reflux,[8] acetic acid in toluene,[30] HCl in ethanol,[31] and H_2SO_4 in ethanol.[32] In addition, they have been synthesized by the condensation of 2-formyl benzoic acid, *o*-phenylenediamine

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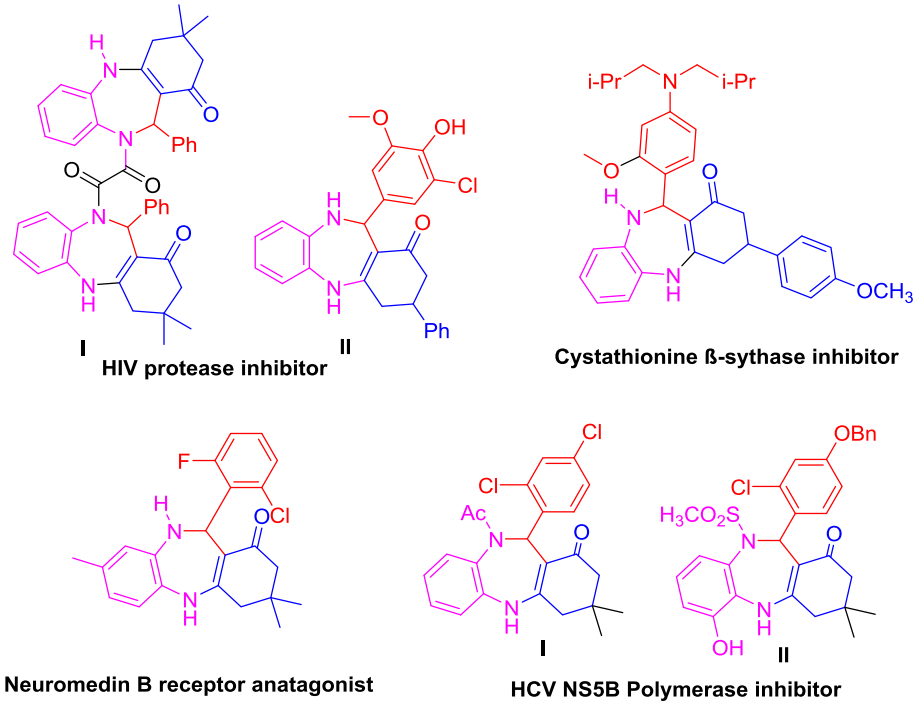

Fig. 1. Pharmacologically active compounds.

and tetronic acid in water under microwave irradiation as a hetero-Cope rearrangement,[33] cycloaddition reaction of 2,2-dihydroxy-1-phenylethanone, *o*-phenylenediamine, and dimedone derivatives.[34]

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,[35] *N*-methyl-2-pyrrolidonium hydrogen sulfate as an ionic liquid,[36] zinc sulfide nanoparticles *via* grinding method,[37] graphene oxide nanosheets,[38] ZnS nanoparticles,[13] ZrO_2-Al_2O_3,[39] chitosan-supported superparamagnetic iron oxide nanocomposite,[40] DES (choline chloride: urea),[41] and promoted by microwaves.[42]

Each of these methods has their own advantages but may suffer from one or more shortcomings such as long reaction time, multistep 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.[43–56] 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 (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 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

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 tempera-