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Current development in multicomponent catalytic synthesis of 1,5-benzodiazepines: A systematic review

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ABSTRACT

1,5-Benzodiazepines are regarded as one of the most important classes of heterocyclic compounds as privileged structures and have vast range of applications in the field of medicine and chemistry. They are therefore attractive synthetic targets for organic and medicinal chemist. The current review article mainly covers the multicomponent green chemistry approaches for the synthesis of 1,5-benzodiazepines. The review is organized systematically into types of catalysts used for the 1,5-benzodiazepines synthesis like silica supported catalysts, various Lewis acids, organoacids and miscellaneous catalysts. This article emphasizes on various heterogeneous and homogenous catalysts used along with their yield and brief description of their mechanism of action. At the end of review, the entire catalyzed are organized into tabulated form for quick at a glance review of various catalysts utilized with their yield and time taken for the synthesis.

Keywords: *1,5-Benzodiazepines, Multicomponent, Silica-supported catalysts, Organoacids, Catalysts.*

1. Introduction

Benzodiazepines (BDZs) are privileged heterocyclic compounds in the field of drugs and pharmaceuticals [1]. They are the drugs of choice in the pharmacotherapy of anxiety and related emotional disorders, sleep disorders, status epilepticus, and other convulsive states; they are used as centrally acting muscles relaxants, for premedication, and as inducing agents in anesthesiology [2].They are the most widely prescribed drugs in current therapeutic use. Among the benzodiazepines, 1,4- and 1,5-benzodiazepines are commonly used as anxiolytic and anticonvulsive drugs. These effects are primarily mediated *via* the benzodiazepine receptors located in the central nervous system. Also peripheral-type benzodiazepine binding sites have been detected in microglia, macrophages and other tissues [3].The number of prescriptions dispensed annually for this class of compounds in the United States is estimated to be in excess of 100,000,000, which, by a conservative estimate, amounts to over 8000 tons.

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Clinically useful benzodiazepines were first synthesized by L. H. Sternbach and his colleagues in the late 1950s [4]. The first commercially available benzodiazepine, chlorodiazepoxide (Librium) was the first benzodiazepine to be synthesized serendipitously in the mid-1950s. Chlordiazepoxide was synthesized from work on a chemical dye, quinazolone-3-oxides. It was discovered by accident when in 1957 tests revealed that the compound had hypnotic, anxiolytic and muscle relaxant effects. Three years later chlorodiazepoxide was marketed as a therapeutic benzodiazepine medication under the brand name Librium. Following chlordiazepoxide, in 1963 diazepam hit the market under the brand name Valium and was followed by many further benzodiazepine compounds over the subsequent years and decades. At the present time, there are approximately one dozen benzodiazepines (including the triazolobenzodiaze-pines and 1,5-benzodiazepines) in therapeutic use worldwide [4].

Benzodiazepines belong to an important class of pharmacologically pre-eminent 1,5-benzodiazepines which have extensively been used as sedative, hypnotic, antidepressant and anticonvulsant [5-8].

Some heterocyclic compounds containing 1,5-benzodiazepines possess anti-inflammatory, analgesic [9], anti-viral [10], anti-HIV [11], anti-microbial [12], anti-tumor [13] activities. More recently their use has been extended to various diseases such as cancer, viral infections (non-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular disorders [14]. Apart from other than biological importance, they are valuable synthons for the preparation of fused ring compounds such as triazolo [15], oxadiazolo [16], oxazino [17], furano [18] benzodiazepines.

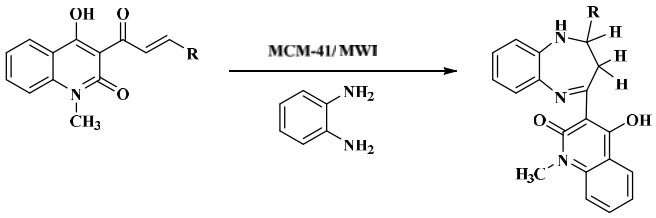
Benzodiazepines bind with high affinity to specific receptors in the brain, which cause an increase in affinity of the neurotransmitter γ-amino butyric acid (GABA). This is known as a $GABA_A$ receptor. The $GABA_A$ receptor is a multi-unit complex with at least six isoforms and 25 subtypes. GABA bind mainly to the α-subunit, while benzodiazepines bind to the β-subunit, called the (BZ-ω) binding site [19]. The γ-subunit is essential for modulation of chlorine transport by benzodiazepines. All benzodiazepines act by enhancing the actions of a natural brain chemical GABA. The GABA receptor is an inhibitory channel which when activated, decreases neuronal activity by increasing the release of Cl^- ions. This natural action of GABA is augmented by benzodiazepines which thus exert an extra inhibitory influence on neurons. Combination of benzodiazepines at the benzodiazepine receptor, situated on the GABA receptor acts as a booster to actions of GABA, allowing more chloride ions to enter the neuron, making it even more resistant to excitation. Several different pharmacological substances can modulate the effect of GABA by binding to GABA receptors. These substances include barbiturates, picrotoxin, certain steroids and even alcohol and they bind to the receptor at different sites from the GABA itself [20,21].

Benzodiazepine and their polycyclic derivatives, in spite of their importance from a pharmaceutical, industrial and synthetic point of view, have comparatively few reviews have been published [22,23]. The following methods are reported in the literature in past decade. The review is organized systematically into types of catalysts used for the 1,5-benzodiazepines synthesis like silica supported catalysts, various Lewis acids, organoacids and miscellaneous catalysts (**Fig. 1**). At the end of review, the entire catalyzed are organized into tabulated form for quick review of various catalysts with their yield and time taken for the synthesis (**Table 1-4**).

2. Literature Review

2.1. Catalytic study of silica supported catalysts in the synthesis of 1,5 benzodiazepines

Sucheta and Rao [24], 2005, described an efficient and operationally simple method for the synthesis of 1,5-benzodiazepine compounds under microwave irradiation versus conventional thermal cyclisation for comparative purposes. Microwave induced organic transformation stands among the alternative routes proposed, so due to various reasons like higher yields in shortest possible time and above all eco-friendliness. The procedure consists of reacting an intimately ground equimolar proportion of *o*-phenylenediamine and α,β-unsaturated enones with silica gel in the presence of catalytic amount of mesoporous zeolite MCM-41 with 90-98% yield **(Scheme 1).**



Scheme 1.

Tajbakhsh *et al* [25], 2006, reported organic synthesis using solid acid heterogeneous catalyzes have been of great interest. For cyclic and acyclic ketones, this procedure is used employing excess ketones, (*o*-phenylenediamine: ketone, 1:4) and in acetonitrile or in dichloromethane solvents. Zeolite catalyst was added to excess of acetone and the mixture stirred for 1 h at room temperature. At this point, the reaction mixture should contain self-condensation product. By addition of *o*-phenylenediamine according to Suschitzky suggested mechanism, the self-condensation product was allowed to react to form the 2,2,4-trimethyl-2,3-dihydro-1,5-benzodiazepine **(Scheme 2).**

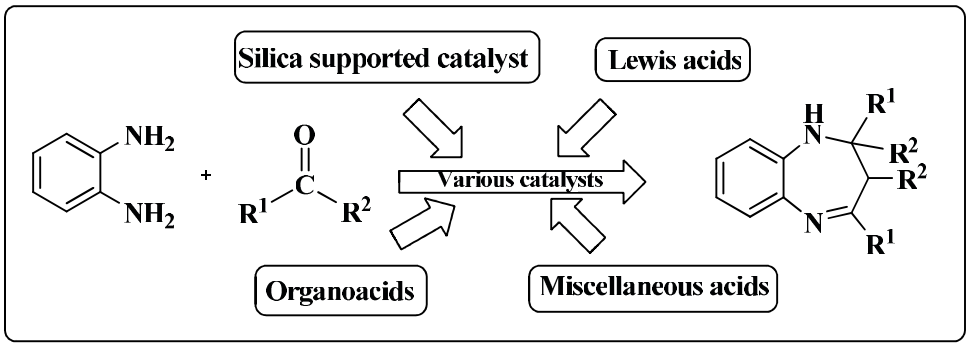
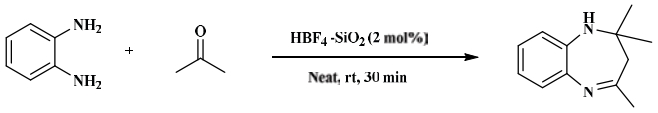


Fig. 1. Various types of catalysts explored for the synthesis of 1,5-benzodiazepines.

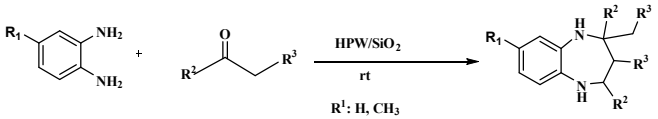
Scheme 2.

Bandgar *et al* [26], 2006, introduced the reaction which was very slow with low yield in the absence of catalyst, while the reaction was slow giving poor yields of the product with silica as a catalyst at 25°C. After doing the optimization of the quantity of the catalyst at room temperature under solvent free conditions and it was observed that the use of just 2 mol% of HBF_4-SiO_2 was sufficient to give the desired products in excellent yields. In unsymmetrical ketone such as 2-butanone, the ring closure occurs selectively only from one side of the carbon skeleton yielding a single product this indicates the selectivity of present method as compared to the reported ones **(Scheme 3).**



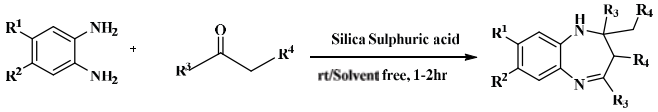
Scheme 3.

Alibeck *et al* [27], 2006, introduced the application of silica supported 12-tungstophosphoric acid (HPW/SiO_2) as solid acid catalyst for the synthesis of 1,5-benzodiazepines by reaction of *o*-phenylenediamines with ketones. After completion of the reaction, the catalyst was easily separated by addition of ethyl acetate and simple filtration. To show reusability of catalyst, the recovered catalyst from the reaction of cyclohexanone was used for the same reaction for thee times. Among the various solid acids, Heteroployacids (HPAs) with keggin structure are widely used as solid acid catalysts due to their very strong Bronsted acidity and their structure properties **(Scheme 4).**



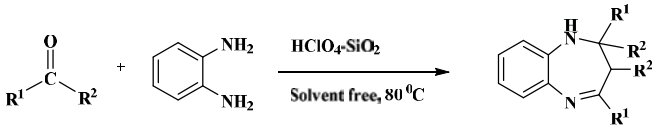
Scheme 4.

Shaabani and Maleki [28], 2007, introduced the new approach for both the linear and cyclic ketones that react with the diamines containing both electron donating and electron-withdrawing groups on aromatic rings, without any significant difference, gave the corresponding 1,5-benzodiazepine derivatives in quantitative yields under solvent-free conditions. A mixture of *o*-phenylenediamine (1 mmol) and acetophenone (2.1 mmol) was stirred at room temperature in the presence of silica sulfuric acid (0.05 g) for 1.2 h to afford 93% pure compound. It is important to note that, starting from unsymmetrical ketones such as 2-butanone, the ring closure occurs selectively only from one side of the carbon skeleton giving a single product. Best results were obtained using 0.05 g of silica sulfuric acid **(Scheme 5).**



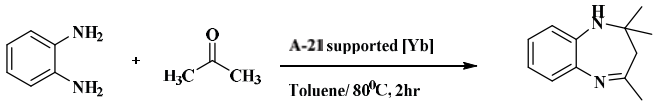
Scheme 5.

Gholap *et al* [29], 2008, described a clean solvent free synthesis of 2, 3-dihydro-(1*H*)-1,5-benzodizepines by condensation of ketones possessing at least one α-hydrogen with *o*-phenylenediamine was mixed, heated and stirred at 80°C temperature catalyzed by silica supported perchloric acid ($HClO_4$-SiO_2) **(Scheme 6).**



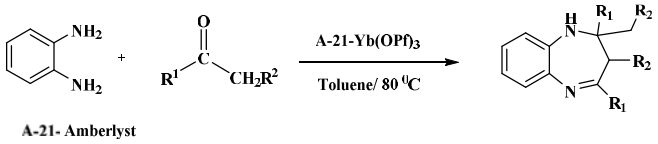
Scheme 6.

Tao and Yi [30], 2008, introduced a method in which Amberlyst-21, a kind of well-known and cheap polymeric material, was treated with ytterbium perfluorooctanesulfonate [Yb $(OPf)_3$] giving a reagent with ytterbium loading of 1.34 (wt%). The polymer-supported fluorousytterbium catalyzed the highly efficient synthesis of 1,5-benzodiazepine derivatives. The catalyst was recovered by simple filtration under fluorous-solvent-free conditions and used again without a significant loss of catalytic activity **(Scheme 7a).**



Scheme 7a.

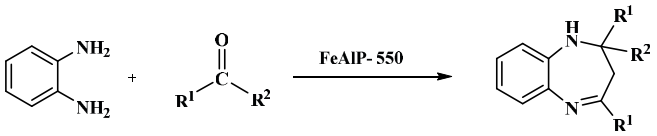
Amberlyst A-21-Yb $(OPf)_3$ was very tolerant and stable to water. The robustness of the catalyst for recycling may partly be attributed to the water repellent nature of the perfluoroalkane chain "$(-CF_2-CF_2-)_n$"of $Yb(OPf)_3$ which refuses the approach of water molecules to the central metal cation, thus maintaining its high catalytic activity **(Scheme 7b).**



Scheme 7b.

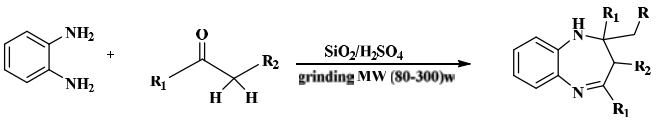
Vijayashankar *et al* [31], 2010, introduced a facile method for the synthesis of 1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones with an amorphous mesoporous iron aluminophosphate (FeAIP) catalyst in the presence of a solvent and under solvent-free conditions heated with stirring in a temperature controlled oil bath at 80°C. The reaction mixture was treated with 1:1 (v/v) water and CH_2Cl_2

and centrifuged to separate the solid catalyst. The organic layer was concentrated and the product was separated by silica gel (100–200 mesh) column chomatography using an ethyl acetate-*n*-hexane (2:8) mixture as eluent **(Scheme 8).**



Scheme 8.

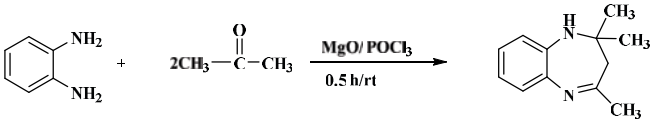
Shushizadeh and Dalband [32], 2012, introduced a green method for the synthesis of 1,5-benzodiazepines by the application of silica resin with acid functional moieties, during which they found that SiO_2/H_2SO_4 mixture was a simple and efficient catalyst for this method under microwave irradiation. This method was a simple, rapid, and high yielding reaction (78–95%) **(Scheme 9).**



Scheme 9.

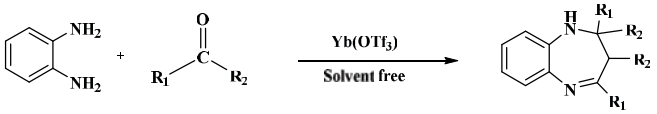
2.2. Catalytic study of various Lewis acids in the synthesis of 1,5 benzodiazepines

Baakrishna and Kaboudin [33], 2001, introduced the solvent free method that had an operationally simple procedure. A mixture of *o*-phenylenediamine, magnesia/phosphorus oxychloride and ketone under solvent-free conditions was capable of producing high yields of 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepines by condensation of *o*-phenylenediamine with acetone under mild reaction conditions in 90% yield **(Scheme 10).**



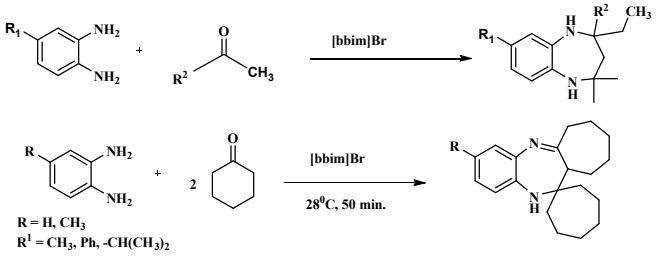
Scheme 10.

Curini *et al* [34], 2001, synthesized 2, 3-Dihydro-1*H*-1, 5 benzodiazepines in very good yield in solvent-free conditions from *o*-phenylendiamine and ketones in the presence of $Yb(OTf)_3$ as catalyst. The method is applicable to both cyclic and acyclic ketones without significant differences **(Scheme 11).**



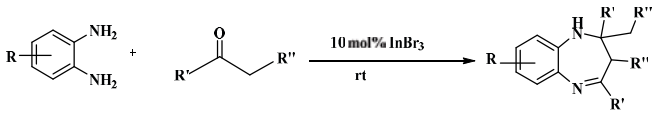
Scheme 11.

Jarikote *et al* [35], 2003, introduced the reaction of *o*-phenylenediamines with both acyclic and cyclic ketones in 1,3-di-*n*-butylimidazolium bromide as an ionic liquid to afford 1,5-benzodiazepines in excellent isolated yields in the absence of a catalyst at ambient temperature **(Scheme 12).**



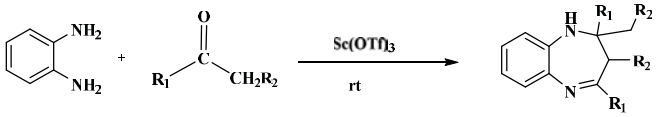
Scheme 12.

Yadav *et al* [36], 2004, introduced a new approach in which treatment of *o*-phenylenediamine with ketone in the presence of 10 mol% indium (III) bromide as Lewis acid for 1.5 h afforded 2, 3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzo [*b*] [1,4]-diazepine in 95% yield. This method was effective for preparation of benzodiazepines from electron deficient *o*-phenylenediamines. The reactions proceeded well at room temperature under solvent free conditions. $InBr_3$ was found to be superior in terms of conversion and reaction rates. This method offers several advantages such as high conversions, short reaction times, clean reaction profiles, high regioselectivity in the case of unsymmetrical ketones **(Scheme 13).**



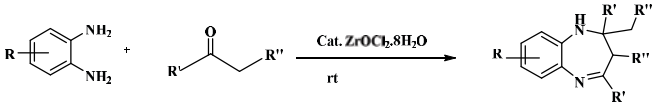
Scheme 13.

De and Gibbs [37], 2005, introduced the reactions which were carried out in neat at room temperature for 3 h by taking a 1:2.2 mol ratio mixture of *o*-phenylenediamine and the ketone in the presence of 5 mol% $Sc(OTf)_3$ to give the desired products in excellent yield **(Scheme 14).**



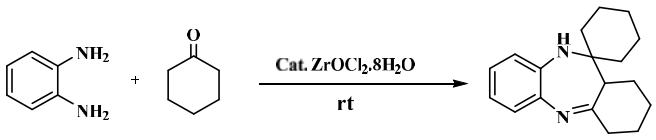
Scheme 14.

Nagawade and Shinde [38], 2006, *o*-phenylene diamines undergo rapid condensation with ketones having hydrogens at the α-position in the presence of 10 mol% zirconyl (IV) chloride under extremely mild reaction conditions to afford the corresponding 1,5-benzodiazepines in excellent yields with high selectivity. This method works well for both electron-rich as well as electron-deficient *o*-phenylenediamines. Zirconyl (IV) chloride is moisture stable, readily available and inexpensive oxy salt of zirconium and versatile lewis acid catalyst. Compared to conventional Lewis acids, zirconyl (IV) chloride has advantages of low amount of catalyst required, moisture stability and catalyst recycling **(Scheme 15a).**



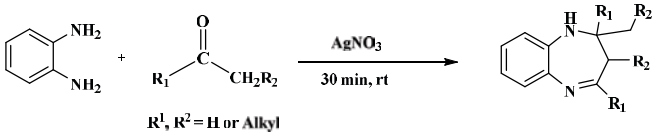
Scheme 15a.

Interestingly, a cyclic ketone such as cyclohexanone also worked well with similar success to afford fused ring 1,5-benzodiazepine in a high yield **(Scheme 15b).**



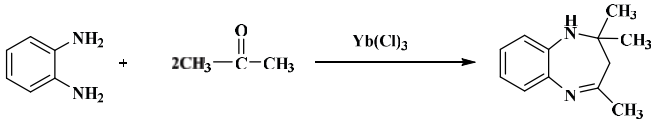
Scheme 15b.

Chandra *et al* [39], 2006, introduced the reactions which were carried out by treating a 1: 2.5 molar ratio mixture of *o*-phenylenediamine and the ketone with a catalytic amount of silver nitrate in a round-bottomed flask, with stirring at room temperature for an appropriate time. The reaction proceeds efficiently under the specified conditions in good to excellent yields. This procedure was successfully extended to other 1,5-benzodiazepine derivatives **(Scheme 16).**



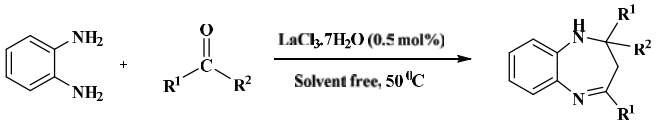
Scheme 16.

Wu [40], 2006, introduced ytterbium trichloride-catalyzed condensation of *o*-phenylenediamines and cyclic and acyclic ketones under solvent-free conditions afforded 1,5-benzodiazepine derivatives in excellent yields **(Scheme 17).**



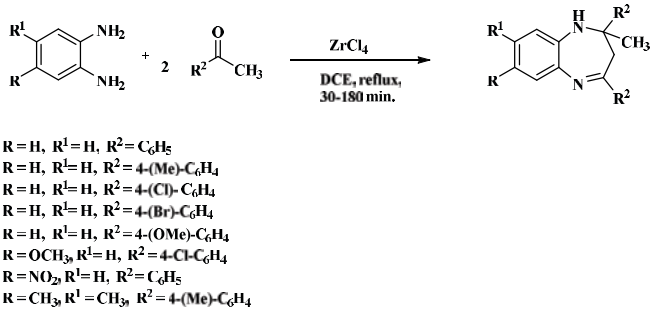
Scheme 17.

Pandit *et al* [41], 2007, reported reaction between *o*-phenylenediamine and aliphatic, aromatic and cyclic ketones in the presence of $LaCl_3 \cdot 7H_2O$ that gave rise to good to excellent isolated yields of the 1,5-benzodiazepines derivatives in relatively short reaction time (30 min) **(Scheme 18).**



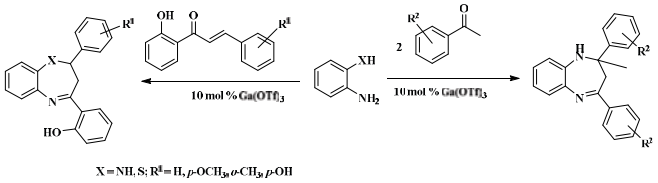
Scheme 18.

Reddy *et al* [42], 2007, reported the catalytic activity of zirconium(IV) tetrachloride for the cyclocondensation reaction of *o*-phenylenediamine and a ketone in refluxing 1,2-dichloroethane to afford the corresponding 2, 3-dihydro-1*H*-1,5-benzodiazepine in high yield. Regarding the optimum quantity of the catalyst, it was found that 10 mol% of catalyst was necessary to promote the reaction with good to excellent yield **(Scheme 19).**



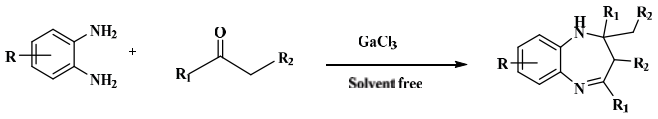
Scheme 19.

Pan *et al* [43], 2008, reported the condensation reactions of *o*-phenylenediamine and two equivalents of acetophenone under gallium (III) triflate catalysis which produced biaryl substituted 1,5-benzodiazepines. Similar reactions of *o*-phenylenediamine or *o*-aminothiophenol and *o*-hydroxy chalcones lead to formation of functionalized 1,5-benzodiazepines and 1,5-benzothiazepines in good to excellent yields. The *o*-hydoxy group of chalcones is crucial for this unprecedented condensation process **(Scheme 20).**



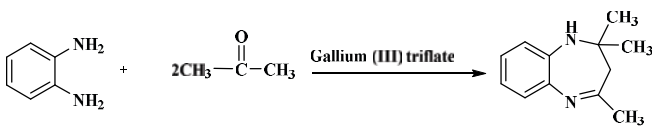
Scheme 20.

Kumar and Shandhu [44], 2008, introduced the use of gallium (III) chloride for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and α-methylene ketones. Diamines with electron releasing and *o*-naphthylenediamine reacted smoothly with ketones to afford products in excellent yields. $GaCl_3$ is an established water scavenger and seems to help both in the formation of imines and the cyclisation step **(Scheme 21).**



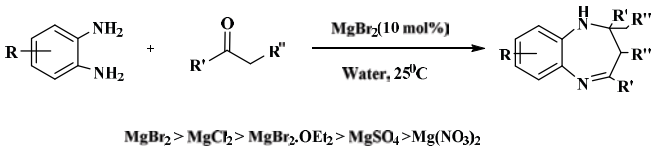
Scheme 21.

Prakash *et al* [45], 2009, introduced the synthesis of 1,5-benzodiazepine derivatives by the condensation of *o*-phenylenediamines and ketones in the presence of gallium (III) triflate in catalytic amount **(Scheme 22).**



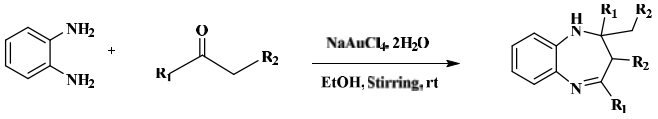
Scheme 22.

Pawar *et al* [46], 2009, reported the reaction of *o*-phenylenediamine (1 mmol) and ketone (1.2 mmol)) in water which was carried in the presence of $MgBr_2$, stirred with respective time at room temperature to afford the corresponding 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine in good yield. The reaction proceeds rapidly at ambient temperature with 10 mol% of catalyst (which is water soluble) and complete within 60 min. By keeping catalyst constant and using different solvents like DCM, CH_3CN, THF, $CHCl_3$, DMSO, DMF, MeOH, EtOH and dioxane afforded a very low yield. Even more, it was investigated the effect of different magnesium salt like $MgCl_2$, $MgBr_2.OEt_2$, $MgSO_4$, and Mg $(NO_3)_2$, but not superior than $MgBr_2$. These results suggest that water is the best solvent for synthesis 2, 3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine, it may be due to catalyst having greater solubility in water than in organic solvent. The $MgBr_2$ was more reactive than other magnesium salt. Various substituted *o*-phenylenediamines and ketones afforded corresponding substituted 1,5-benzodiazepine products in very good to excellent yields. All the reactions were completed within 40–60 min **(Scheme 23).**



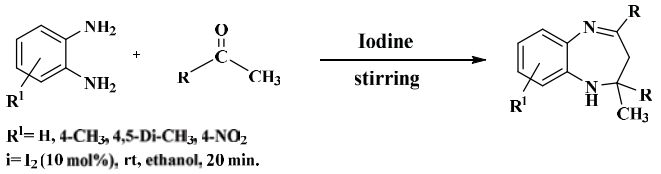
Scheme 23.

Shi *et al* [47], 2010, described an efficient and clean method for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and ketones catalyzed by sodium tetrachloroaurate(III) dihydrate under mild conditions. The catalyst was shown to be equally effective for the synthesis of quinoxalines from *o*-phenylenediamine and α-bromo ketones under the similar reaction conditions. This method produced good yields **(Scheme 24).**



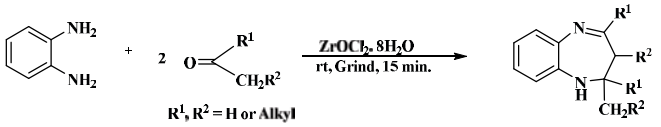
Scheme 24.

Parveen *et al* [48], 2011, described the synthesis of 2, 3-dihydro-1*H*-1,5-benzodiazepine by taking a solution of OPD/substituted OPD and the ketone in I_2 (10 mol%) by adding 3-4 drops of ethanol for well mixing and stirred at ambient temperature for appropriate time. Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amount **(Scheme 25).**



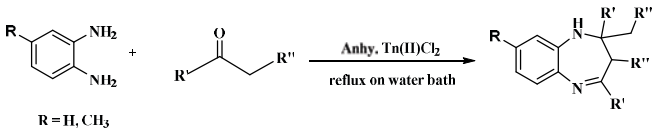
Scheme 25.

Baseer and Khan [49], 2011, introduced a method in which zirconium oxychloride efficiently catalyzed the condensation of ketones (cyclic and acyclic) with *o*-phenylenediamine at room temperature, under solvent free conditions, in short reaction time with excellent yield of the product. *o*-Phenylenediamine (OPD), ketones and zirconium oxychloride (catalytic amount) were ground well using mortar and pestle at room temperature, the corresponding 1,5-benzodiazepineand fused ring benzodiazepine derivatives were obtained in 80-85% yield, whereas ZrO_2 gave very low yield **(Scheme 26).**



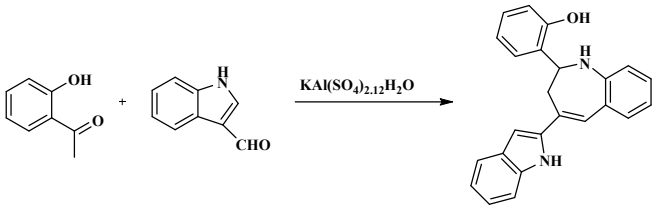
Scheme 26.

Sharma et al [50], 2011, designed the synthesis of benzodiazepines using anhydrous tin(II) chloride as efficient catalyst in which substituted ketone (20 mmoles), *o*-phenylenediamine (10 mmoles), and tin(II) chloride anhydrous (0.5 mmoles) were ground well using mortar and pestle and transferred to a 50 ml round bottomed flask and heated at 80-85°C for 40 min to 1h. The precipitated solid was separated, washed thoroughly water and dried. The product was recrystallised from ethanol to get the pure 2,3-dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-benzodiazepine **(Scheme 27)**.



Scheme 27.

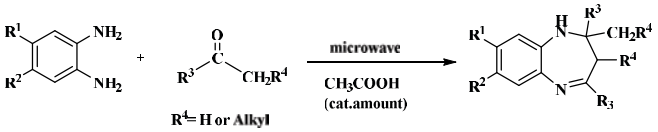
Singla *et al* [51], 2012 reported a simple and versatile method for the synthesis of 1,5-benzodiazepines *via* condensation of *o*-phenylenediamines and ketones in the presence of catalytic amount of potassium aluminium sulfate dodecahydrate ($KAl(SO_4)_2.12H_2O$) as a non-toxic and inexpensive catalyst **(Scheme 28).**



Scheme 28.

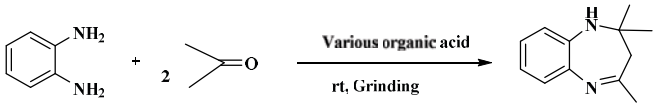
2.3. Catalytic study of various organoacids in the synthesis of 1,5 benzodiazepines

Pozarentzi *et al* [52], 2002, reported a facile synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by condensation of ketones with *o*-phenylenediamines by application of microwave irradiation without using solvent. In conclusion, it was described as a rapid and efficient synthesis **(Scheme 29).**



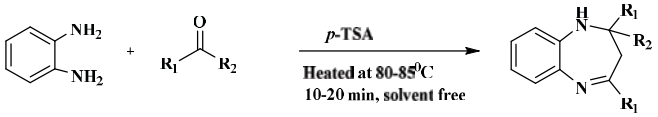
Scheme 29.

Thakuria *et al* [53], 2006, introduced one pot method for the synthesis of a 2, 3-dihydro-1,5-benzodiazepines by the condensation of acetone with *o*-phenylenediamine using an organic acid as the catalyst under solvent-free conditions at room temperature. The other acids used are anthanilic acid, isonicotinic acid, malonic acid, adipic acid, valeric acid, citric acid, iminodiacetic acid but the best results were obtained using 1,3,5-benzene-tri-carboxylic acid (trimesic acid) as catalyst **(Scheme 30).**



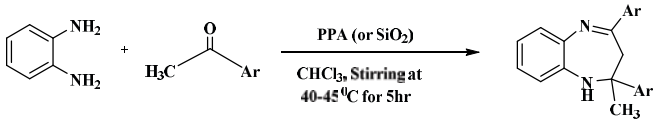
Scheme 30.

Pasha and Jayashankara [54], 2006, reported synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by the condensation of *o*-phenylenediamine with cyclic/ acyclic ketones in the presence of *p*-toluenesulfonic acid (*p*-TSA) as catalyst at 80-85°C temperature. The yields were high and reactions were completed within 10-20 min. *p*-TSA, which was an inexpensive and common organic acid, can efficiently catalyze this reaction **(Scheme 31).**

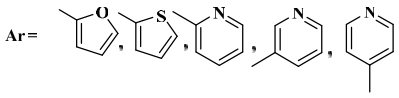


Scheme 31.

Jung *et al* [55], 2007, reported the synthesis of 1*H*-1,5-benzodiazepine derivatives with heteroaromatic ketone (2-acetylfuran, 2-acetylthiophene, 2-acetylpyridine, 3-acetylpyridine, 4-acetylpyridine) by using *conc.* HCl, SiO_2, or polyphosphoric acid (PPA). When 1,2-phenylenediamine (2.5×10^{-2} mol) was treated with heteroaromatic ketones (5×10^{-2} mol) in the presence of PPA (0.16 g) at 40-45°C for 5 h, a yellow crystalline solid was isolated in 48% yield **(Scheme 32a).**

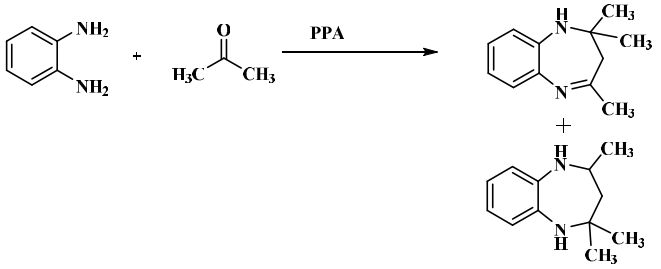


Scheme 32a



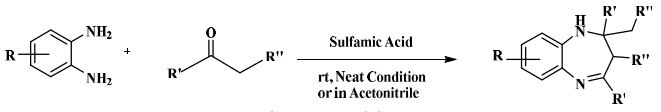
Scheme 32a.

In case of the reaction of 4-chloro-1,2-phenylenediamine with acetone, after the separation and precise characterization, 7-chloro-2,2,4-trimethyl-2, 3-dihydro-1*H*-1,5-benzodiazepine and 8-chloro-2,2,4-trimethyl-2, 3-dihydro-1*H*-1,5-benzodiazepine were obtained as structural isomers **(Scheme 32b).**



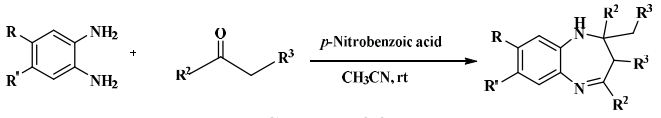
Scheme 32b.

Zhenjiang *et al* [56], 2007, synthesized 2, 3-dihydro-1*H*-1,5-benzodiazepines in good to excellent yield from direct condensation of *o*-phenylenediamines with ketones promoted by sulfamic acid at room temperature under neat condition or in acetonitrile **(Scheme 33).**



Scheme 33.

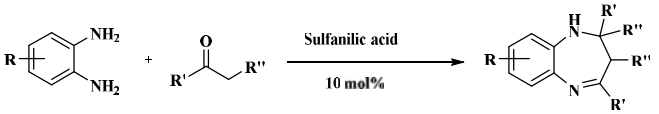
Varala *et al* [57], 2007, introduced *p*-nitrobenzoic acid promoted synthesis of 1,5-benzodiazepines by taking a mixture of *o*-phenylenediamine and cyclic and acyclic ketones.The other acids used are benzoic acid, phenylacetic acid, mandelic acid, anthanilic acid, isonicotinic acid, malonic acid, adipic acid, valeric acid, citric acid, iminodiacetic acid etc**(Scheme 34).**



Scheme 34.

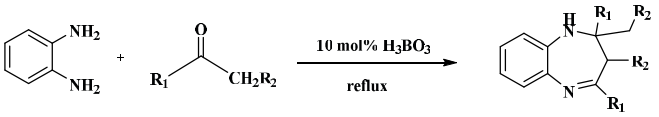
Sangshetti *et al* [58], 2007, reported the synthesis of 1,5-benzodiazepines using *o*-phenylenediamine and the ketone substrates and varying the mol% of sulfanilic

acid. Among the results obtained, using 10 mol% sulfanilic acid gave better yield (97%) for the synthesis **(Scheme 35).**



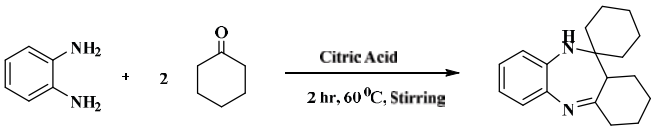
Scheme 35.

Zhou *et al* [59], 2009, introduced the synthesis which was carried out by mixing *o*-phenylenediamine with ketones in the presence of a catalytic amount of boric acid in *n*-hexane. When the amount of catalyst used was less than 10 mol%, yields of benzodiazepine derivatives were decreased due to incomplete conversion of substrates and any excess of catalyst beyond this proportion (10 mol%) did not show any further increase in conversion and yields **(Scheme 36).**



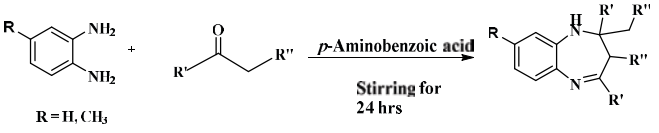
Scheme 36.

Baseer and Khan [60], 2011, introduced citric acid catalyzed condensation of ketones (cyclic and acyclic) with *o*-phenylenediamine at 60°C, under solvent free conditions, in short reaction time (2h) with excellent yield of the product 75-85% **(Scheme 37).**



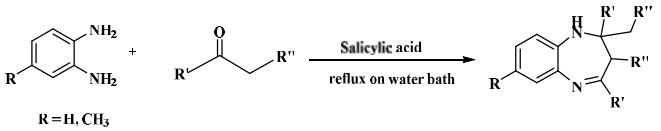
Scheme 37.

Sandhar *et al* [61], 2012, screened various aminoacids for the synthesis of 1,5-benzodiazepines in which *p*-aminobenzoic acid was found to be the versatile catalyst for the preparation of 1,5-benzodiazepine derivatives from a wide range of substituted *o*-phenylenediamines and ketones by stirring for 24 h. The corresponding products were obtained in good isolated yields (85-92%) at room temperature under solvent-free conditions **(Scheme 38).**



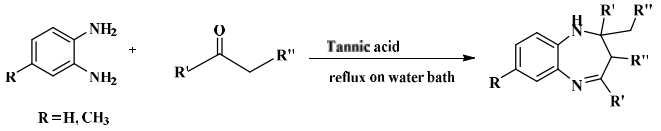
Scheme 38.

Sandhar *et al* [62], 2012, introduced a rapid and efficient environment friendly one-pot synthesis of 2, 3-dihydro-1*H*-1,5-benzodiazepines catalyzed by salicylic acid has been described under solvent free condition by simple condensation of *o*-phenylenediamine with different ketones. Simple and effective method, use of non-hazardous and cheap catalyst and good to excellent yields (85-94%) are the important features of this method **(Scheme 39).**



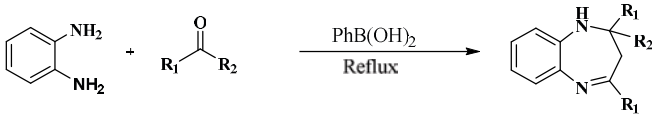
Scheme 39.

Sandhar and Singh [63], 2012, introduced a rapid and efficient environment friendly multicomponent one-pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines catalyzed by tannic acid under solvent free condition by simple condensation of *o*-phenylenediamine with different ketones. The advantages of this green protocol were high yield, short reaction time, clean reaction profile, simple work up, environmentally benign procedure under solvent-free conditions **(Scheme 40).**



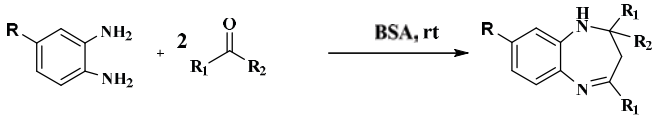
Scheme 40.

Goswami *et al* [64], 2013, introduced the synthesis of 1,5-benzodizepine *via* condensation of *o*-phenylenediamine with ketone in the presence of catalytic amount of phenylbronic acid in acetonitrile solvent under reflux condition, yield 82-91% **(Scheme 41).**



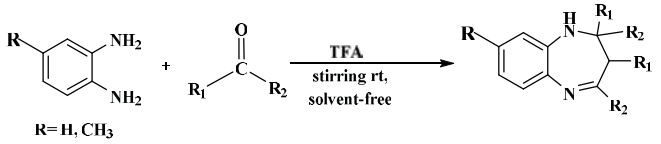
Scheme 41.

Sajadiffer and Rezayati [65], 2013, described the synthesis of 1,5-benzodizepine derivatives using boron sulfonic acid, yield 85-99% **(Scheme 42).**



Scheme 42.

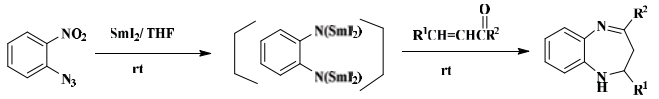
Zhao *et al* [66], 2014, described the one-pot three-components condensation reaction of *o*-phenylene diamines with α,β-unsaturated carbonyl compounds to form a derivatives of 1,5-benzodiazepines by using TFA (trifluoroacetic acid) as a catalyst. TFA has low toxicity, good solubility in water and organic solvents. The advantages of this protocol were easy work out, no solvent requirement, mild reaction condition and excellent yield (85-94%) (**Scheme 43).**



Scheme 43.

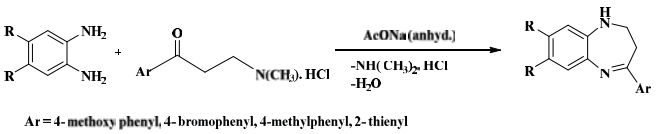
2.4. Catalytic study of miscellaneous acids in the synthesis of 1, 5 benzodiazepines

Chen *et al* [67], 2001, introduced applications of samarium diiodide (SmI_2) as a mild, neutral, selective and versatile single-electron transfer reducing and coupling reagent in organicsynthesis which has grown significantly in the last decade. When *o*-nitrophenylazide was treated with SmI_2 at room temperature, the simultaneous reduction of nitro group and azide group resulted in the formation of trivalent samarium species. According to the literature, the trivalent samarium species was considered as the intermediate (samarium amide) which was "living" double-anion *in situ* and might react smoothly with α,β-unsaturated ketones to afford 2, 3-dihydro-1*H*-1,5-benzodiazepines **(Scheme 44).**



Scheme 44.

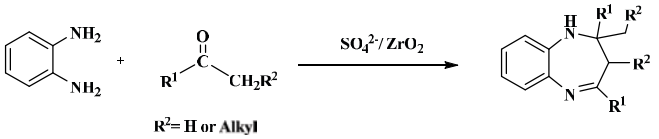
Roman *et al* [68], 2002, synthesized 4-aryl-2,3-dihydro-1*H*-1,5-benzodiazepines by cyclocondensation of ketonic Mannich bases hydrochlorides with *o*-arylenediamines and reactions proceeded smoothly in ethanol in the presence of anhydrous sodium acetate which led to fused diazepines. The use of ethanol instead of aromatic hydrocarbons ensured mild reaction conditions, short reaction times and an easy separation of the products from the reaction mixture. However, the yields of fused diazepines, obtained *via* a base-catalyzed cyclocondensation, are comparable with those reported when the reaction was carried out without any catalyst **(Scheme 45).**



Ar = 4- methoxy phenyl, 4- bromophenyl, 4-methylphenyl, 2- thienyl

Scheme 45.

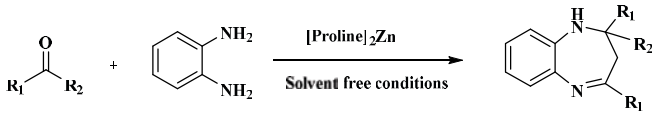
Reddy *et al* [69], 2003, synthesized 2, 3-dihydro-1*H*-1,5-benzodiazepines by taking a 1:2.5 mole ratio mixture of *o*-phenylenediamine and the ketone along with a catalytic amount of sulfated zirconia in a round bottom flask with stirring at ambient conditions for the appropriate time **(Scheme 46).**



R2= H or Alkyl

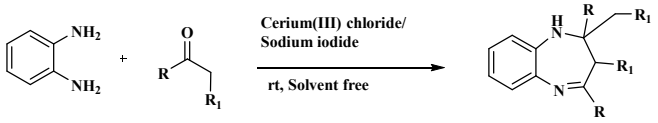
Scheme 46.

Sivamurugan *et al* [70], 2004, carried out the synthesis of 2, 3-dihydro-1*H*-1,5-benzodiazepines by mixing *o*-phenylenediamine with ketones in the presence of a catalytic amount of $[Proline]_2Zn$ **(Scheme 47).**



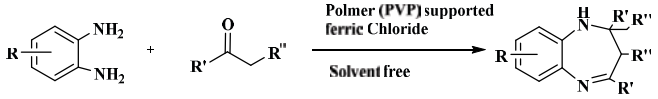
Scheme 47.

Gowravaram *et al* [71], 2004, introduced a novel and green approach for the synthesis of 2, 3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamines and ketones using cerium (III) chloride/ sodium iodide under mild and heterogeneous conditions. The reactions were carried out at room temperature without using any organic solvent **(Scheme 48).**



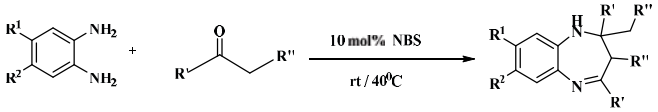
Scheme 48.

Chari and Syamsundar [72], 2005, introduced a new procedure in which polymer (PVP) supported ferric chloride catalyzed efficiently the condensation of *o*-phenylenediamines with ketones under solvent free conditions to afford the corresponding 1,5-benzodiazepine derivatives in high yields. The reaction proceeded efficiently under ambient conditions giving excellent yields (85–96%) **(Scheme 49).**



Scheme 49.

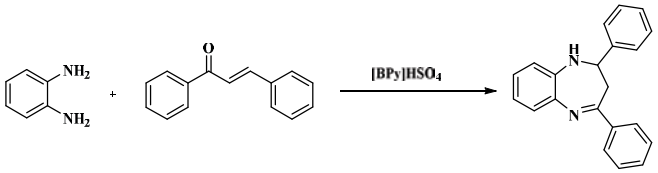
Kuo *et al* [73], 2006, introduced the reaction which was performed by reacting *o*-phenylenediamine and acetone in the presence of 2 mol% NBS as a catalyst without any solvent at room temperature. Under these conditions, 1,5-benzodiazepine was obtained in 83% yield after 2 h reaction. Only a trace amount of product was obtained in the absence of a catalyst, even when the reaction time was extended to 24 h, thus demonstrating the importance of NBS. In the case of the strong electron donating 4-methoxy acetophenone, a longer reaction time was observed, whereas in the case of heterocyclic ketones such as 2-acetylthiophene also has good yields **(Scheme 50).**



Scheme 50.

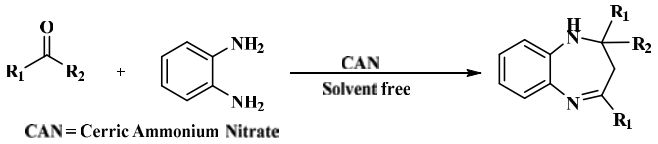
Yuying *et al* [74], 2006, introduced a novel and simple ionic liquid methodology for the synthesis of 1,5-benzodiazepines. 1-Butylpyridinium hydrogen sulphate ($[BPy]HSO_4$), an acidic room-temperature ionic liquid, as a novel and efficient catalyst, was synthesized and used in the preparation of a series of 1,5-benzodiazepine derivatives by the reaction of *o*-phenylenediamine with chalcones under mild

conditions. This method was easy, efficient, environmentally friendly, and economical, free of toxic catalyst, and has good yields for the formation of 1,5-benzodiazepines **(Scheme 51).**



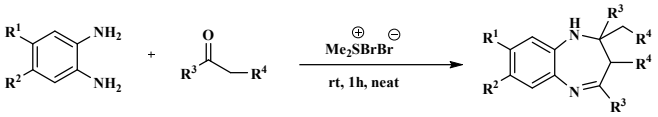
Scheme 51.

Varala *et al* [75], 2006, introduced ceric ammonium nitrate (CAN) as an efficient reagent for the preparation of 1,5-benzodiazepine derivatives of a wide range of substituted *o*-phenylenediamines and electronically divergent ketones in moderate to excellent isolated yields (60-98%) under mild conditions using methanol as solvent at ambient temperature **(Scheme 52).**



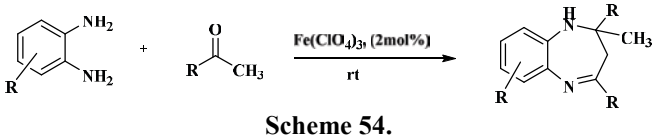
Scheme 52.

Das *et al* [76], 2006, reported an efficient solvent-free synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamines with ketones in the presence of catalytic amount of bromodimethylsulfonium bromide. The condensation occurred at room temperature and the products were formed in high yields **(Scheme 53).**



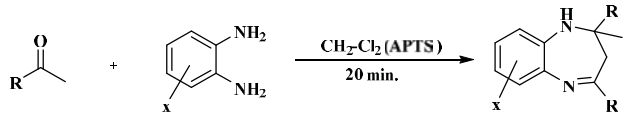
Scheme 53.

Heravi *et al* [77], 2006, synthesized 2, 3-dihydro-1*H*-1,5-benzodiazepines by condensation of *o*-phenylendiamine and various ketones in the presence of ferric perchlorate ($Fe(ClO_4)_3$) under solvent free conditions **(Scheme 54).**



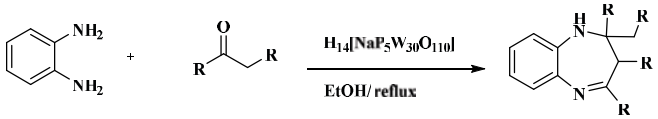
Scheme 54.

Guzen *et al* [78], 2006, reported a new method for the synthesis of 1,5-benzodiazepines which were synthesized by a reaction of *o*-phenylenediamines with a diketone or ketone series by ultrasound irradiation in presence of APTS. The condensation occurred in a mild condition with good to excellent yields **(Scheme 55).**



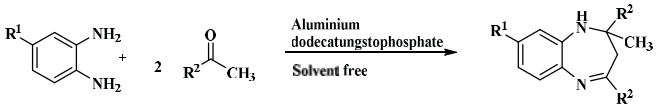
Scheme 55.

Heravi *et al* [79], 2007, reported a new method in which mixture of ketone, *o*-phenylenediamine derivative and $H_{14}[NaP_5W_{30}O_{110}]$ (0.1 mol %) was refluxed in ethanol at 78°C. But in the case of cyclohexanone as a cyclic ketone the reaction times were longer than others, it may be because of the steric effect of cyclic ketones. The catalyst serves as a green recyclable and heterogeneous catalyst **(Scheme 56).**



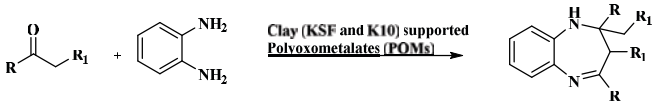
Scheme 56.

Fazaeli and Aliyan [80], 2007, introduced aluminium dodecatungstophosphate promoted synthesis of 1,5-benzodiazepine derivatives under solvent free conditions **(Scheme 57).**



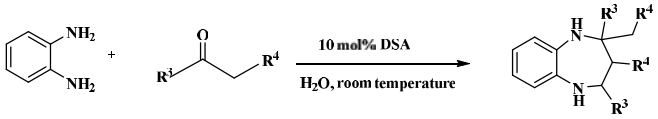
Scheme 57.

Fazaeli and Aliyan [81], 2007, introduced a simple and versatile method for the synthesis of 1,5-benzodiazepines *via* condensation of 1,2-phenylenediamines and ketones in the presence of catalytic amount of clay (K10 and KSF montmorillonite)-supported polyoxometalates (POMs). The method was applicable to both cyclic and acyclicketones without significant differences. The reaction proceeded efficiently under ambient conditions with good to excellent yields (**Scheme 58).**



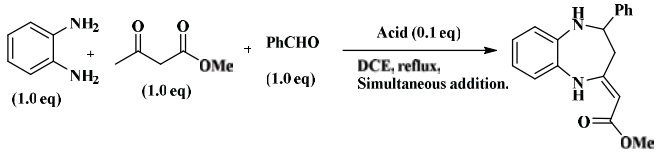
Scheme 58.

Sharma *et al* [82], 2007, introduced a simple, efficient, mild and green method which has been developed for the synthesis of 1,5-benzodiazepines employing dodecyl sulfonic acid (DSA) as an excellent surfactant-type Bronsted acid catalyst in aqueous media at room temperature **(Scheme 59).**



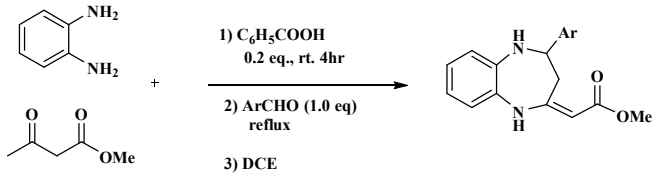
Scheme 59.

Murai *et al* [83], 2008, reported the novel thee-component reaction of aromatic aldehydes, ethylenediamine, and β-keto esters producing seven-membered 1,4-azepane compounds. This reaction was very unique because β-keto esters reacted at the generally unreactive γ-positions. The reaction mechanism was rationalized as follows: during the first stage of the reaction, ethylenediamine bridges the aldehyde and the β-keto esters to form the intermediates involving imines and enamino esters. Next, the intramolecular reaction of the intermediate occurs between the imine and γ-position of the enamino ester. In this one-pot thee-component reaction 1,2-phenylenediamine was used instead of ethylenediamine **(Scheme 60a).**



Scheme 60a.

In this reaction 1.0 equiv of 1,2-phenylenediamine and benzaldehyde, 1.3 equiv of methyl acetoacetate and 0.2 equiv of C_6H_5COOH was used and gave the best results. Various benzaldehydes having the substituent at the para position were examined. Although electron-withdrawing groups gave much better results, both the electron-donating and electron withdrawing groups gave moderate yields. The result of using *o*-methyl benzaldehyde indicated that this reaction was more influenced by steric effects. Furthermore, not only various substituted benzaldehydes, but also 2-naphthaldehyde, 3-furancarboxaldehyde and 2- thiophenecarboxaldehyde were applicable. Various β-keto esters were next examined using 1,2-phenylenediamine and benzaldehyde. Not only benzyl acetoacetate, but also tert-butyl acetoacetate having the acid sensitive tert-butyl ester moiety was tolerant and gave good results. The main feature of this reaction was the γ-selective C–C bond formation of β-enamino esters probably due to the thermodynamic control derived from intramolecular hydrogen bonding of the enamino esters **(Scheme 60b).**

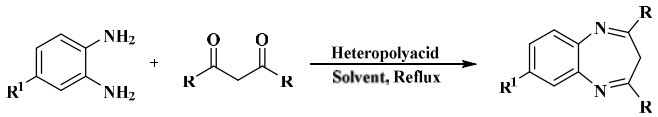


Scheme 60b.

Mahajan *et al* [84], 2008, introduced the synthesis of 1,5-benzodiazepine from the condensation of 1 mole of *o*-phenylenediamine with 2 moles of ketone under solvent-free conditions catalyzed by alum [$KAl(SO_4)_2{\cdot}12H_2O$] which was found to be an efficient, non-toxic, cheap, and environmentally benign and gave good to excellent yields **(Scheme 61).**

Scheme 61.

Heravi *et al* [85], 2008, reported a simple method for the condensation of *o*-phenylenediamines (*o*-PDA) with 1,3-diketones using catalytic amounts of different types of HPAs including $H_{14}[NaP_5W_{30}O_{110}]$, $H_5[PMo_{10}V_2O_{40}]$ and $H_6[P_2W_{18}O_{62}]$ as the catalyst to synthesize 3*H*-1,5-benzodiazepines. The presence of an electron-donating or an electron-withdrawing group on the aromatic ring of *o*-PDA affected the reaction yields. An electron-withdrawing group decreases the yield of the reaction but an electron-donating group increased it. The steric effect of phenyl groups of 1,3-diphenyl-propane-1,3-dione contribute to lower yields of reaction **(Scheme 62).**

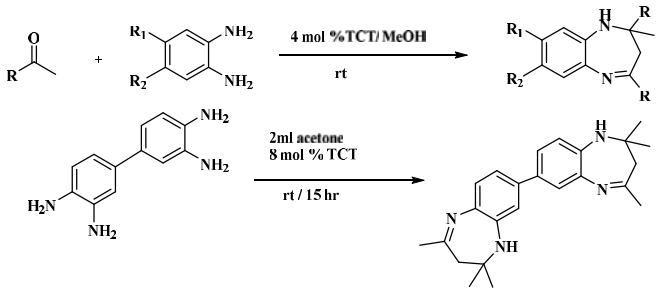


Scheme 62.

Li-Tao *et al* [86], 2008, introduced the synthesis of 2, 3-Dihydro-1*H*-1,5-benzodiazepines which have been synthesized under solvent-free conditions in good yields from *o*-phenylenediamine and ketones catalyzed by montmorillonite K10. This method has advantages of mild reaction conditions, simple operation and environmental friendliness **(Scheme 63).**

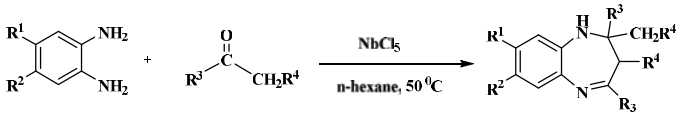
Scheme 63.

Kuo *et al* [87], 2008, introduced 2,4,6-trichloro-1,3,5-triazine (TCT) efficiently catalyzed the condensation reactions between 1,2-diamines and various enolizable ketones to afford 1,5-benzodiazepines in good to excellent yields. 2,4,6-trichloro-1,3,5-triazine (TCT) has received considerable attention due to its commercial availability and efficient delivery of anhydrous HCl in reaction media. The HCl generated *in situ* acts as a protic acid, activates the carbonyl oxygen to promote the condensation to give the products. The *o*-phenylenediamine (1 equiv.) and acetone (2.5 equiv.) were stirred at ambient temperature in dichloromethane with 4 mol% of TCT. The reaction was complete within 5.5 h. After screening various solvents like methanol, ethanol, isopropanol, ethyl acetate and acetonitrile, it was found that the reaction proceeded well in polar solvents, giving slight variations in reaction time and methanol was the best choice for this reaction **(Scheme 64).**



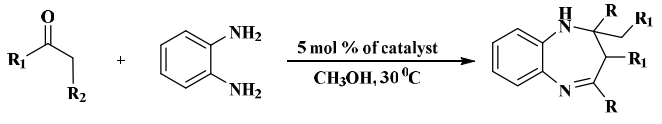
Scheme 64.

Gao *et al* [88], 2009, introduced the synthesis of 1,5-benzodiazepine derivatives in moderate to excellent isolated yields by the condensation reactions of *o*-phenylenediamine and ketones catalyzed by Niobium pentachloride ($NbCl_5$) under mild conditions using *n*-hexane as solvent at 50°C. This method is simple and effective with good yields **(Scheme 65).**



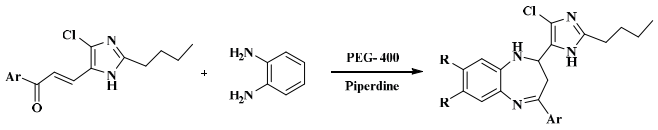
Scheme 65.

Gopalakrishanapanicker *et al* [89], 2009, reported a method in which tetranitrile silver complex was prepared and used as homogeneous catalyst for one pot thee component Mannich reaction and benzodiazepine synthesis from *o*-phenylenediamine and various ketones. The Ag complex is able to catalyze two mechanistically distinct reactions of synthetic importance under mild conditions. Homogeneous catalyzes using organometallic complexes is advancing into the modern fine chemical and bulk chemical industries. This catalyst eliminates the requirement of pre-formed imines and enolates for obtaining good results. The tetranitrile ligand used to prepare the catalyst was Propylenediamine tetrapropionitrile. The reactions proceeded efficiently with good yields. The catalyst can be separated from the product by changing the solvents. The tetranitrile-silver complex (0.25 mmol) was prepared in methanol (5 ml). To this solution aldehyde (5 mmol), ketone (5 mmol) and aniline (5.1 mmol) were added and stirred at room temperature **(Scheme 66).**



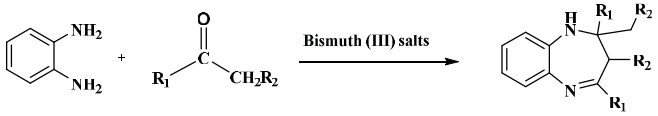
Scheme 66.

Konda *et al* [90], 2011, described a new method in which a mixture of substituted chalcone (1 mmol), *o*-phenylenediamine (1.5 mmol) and piperidine (1 ml) in polyethylene glycol (PEG-400) (15 mL) was heated at 60°C. After completion of reaction (TLC), the reaction mixture was extracted with ethyl acetate. The combined organic layers obtained product was recrystallized by aqueous acetic acid to give pure product. PEG-400 was recovered and further used for next run **(Scheme 67).**



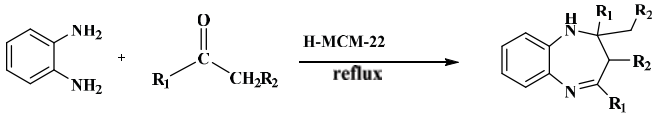
Scheme 67.

Chaskar *et al* [91], 2011, reported bismuth (III) salts catalyzed synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepine from *o*-phenylenediamine and acyclic and cyclic and aromatic ketones in mild conditions **(Scheme 68).**



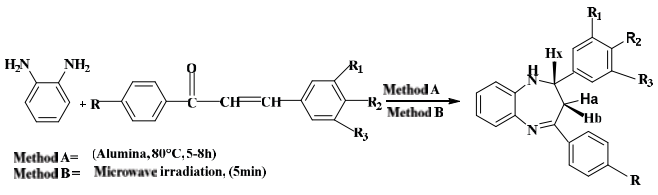
Scheme 68.

Majid *et al* [92], 2012, reported a simple and versatile method for the synthesis of 1,5-benzodiazepines is *via* condensation of *o*-phenylenediamines and ketones in the presence of catalytic amount of H-MCM-22 using acetonitrile as solvent at room temperature. In all the cases, the reactions were highly selective and were completed within 1–3h. The method was applicable to both cyclic and acyclic ketones without significant differences. The reaction proceeded efficiently under ambient conditions with good to excellent yields **(Scheme 69).**



Scheme 69.

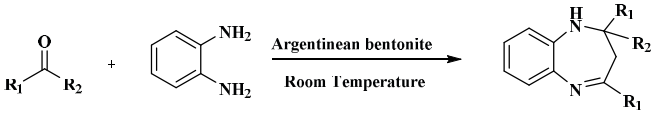
Sharma and Joshi [93], 2012, described the synthesis of 2,4-disubstituted-1,5 benzodiazepines under refluxing (Method A) and microwave condition (Method B).Yield-(Method A: 38-58%) (Method B: 58-86%) **(Scheme 70).**



Scheme 70.

Makone and Vayavahare [94], 2012, introduced sodium perchlorate as an efficient agent for the preparation of 2,3-dihydro-1H-1,5-benzodiazepine derivatives by the condensation of *o*-phylenediamine and various ketones in the presence of stoichiometric amount of $NaClO_4$ in an aqueous media.

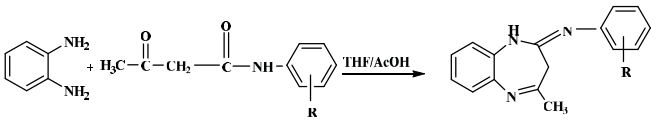
Munoz *et al* [95], 2012, explored the catalytic activity of argentinean bentonite as catalysts for the synthesis of 1,5-benzodiazepines though a condensation reaction between *o*-phenylenediamine and excess of acetone as reactive and solvent at room temperature. The catalysts were found to be highly active and selective, affording a high yield of the corresponding benzodiazepines in short reaction time of 1-3 h. The catalyst showed excellent activity showing 86–90% isolated yields. The easy work-up procedure and the recyclable catalyst make this methodology attractive for large-scale operations (**Scheme 71**)



Scheme 71.

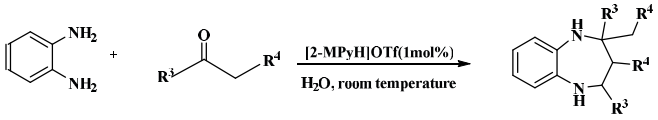
Based on this, **Kurane *et al* [96], 2013**, designed an ionic liquid film of [Bmim]Cl containing an organometallic catalyst (Cp_2ZrCl_2) has been anchored on the porous matrix of an aerogel by adsorption interactions and successfully used for the synthesis of medicinally relevant 1,5-benzodiazepines.

Ilango *et al* [97], 2013, described the synthesis of (4-methyl-1,5-dihydro-1,5 benzodiazepine-2-ylidene)-aryl-amines using *o*-phenylenediamine and acetoacetanilide catalyzed by $CdCl_2$ under thermal and microwave irradiation. These compounds show good antibacterial and antifungal activities **(Scheme 72).**



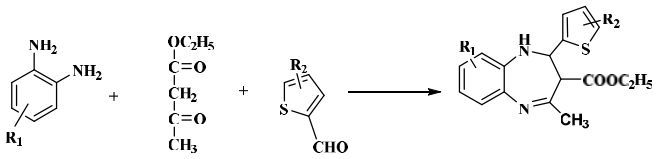
Scheme 72.

Alinezhad *et al* [98], 2013, described the synthesis of 1,5-benzodizepinederivative using (2-MPyH)OTf as a catalyst. They reported a method for synthesis of 1,5-benzodizapine derivatives in high yield 93-98% and short reaction time (25-15 min) **(Scheme 73).**



Scheme 73.

Li and Wang [99], 2014, introduced the one pot synthesis of 1, 5 benzodizepine derivative containing thiophene and $COOCH_2CH_3$ groups. The reaction preceded by thee component condensation of substituted thiophene carboxaldehyde, *o*-phenylenediamine and ethylacetoacetate in ethanol at 0°C with yield 86-92% **(Scheme74).**



Scheme 74.

3. Mechanism of action of catalysts

All homogenous and heterogeneous catalysts catalyzed the reaction by the activations of both *o*-phenylenediamine and ketones. At one place, catalyst initiated electrophilic activation of the carbonyl groups of ketones by coordinated to oxygen making them susceptible to nucleophilic attack by amines giving the intermediate diimine A. A 1,3-hydrogen shift of the attached methyl group then occurs to form an isomeric enamine **B**, which cyclize to afford seven membered ring with the generation of catalyst (**Fig. 2**).

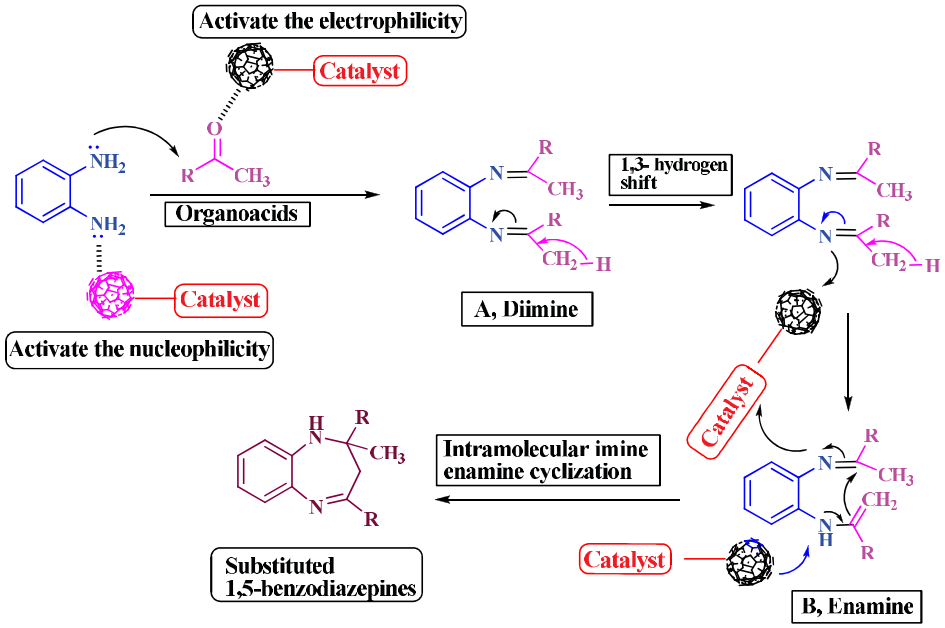


Fig. 2. Mechanism of action of synthesis of 1,5-benzodiazepines promoted by various types of catalyst.

4. Conclusion

Benzodiazepines have gained great attention in the area of synthetic medicinal chemistry. It has also pharmaceutical and industrial application. So there is always a strong need for exploration of novel catalysts and development of efficient technique for the synthesis of 1,5-benzodiazepines. Developing environmental friendly and effective technologies coupled with green chemistry is a major area of concern for chemical community. In this review, we have focused on green catalytic approaches for an environment-friendly synthesis of 1,5-benzodiazepines. Our knowledge of exploring novel catalysts should aid in future research to synthesize various other 1,5-benzodiazepine derivatives having diverse pharmacological actions.

Table 1. Catalytic study of silica supported acids in the synthesis of 1,5 benzodiazepines.

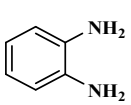
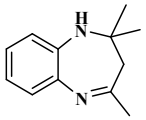
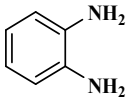
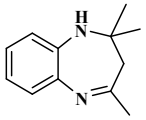
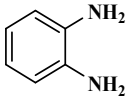
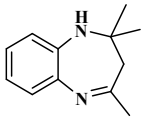
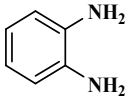
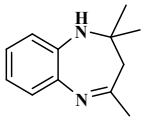
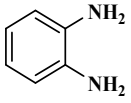
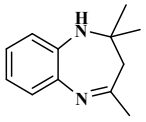
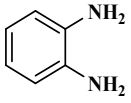
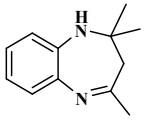
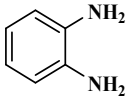
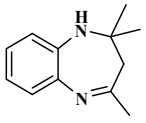
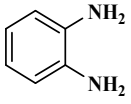
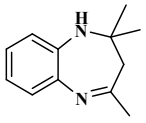
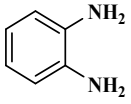
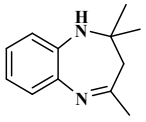
Entry	Diamine	Ketone	Product	Catalyst	Time	Yield (%)
1				MCM-41 Zeolite [24]	8 h	90-98%
2				Zeolite catalyst [25]	1 h	65-80%
3				HBF_4-SiO_2 [26]	30 min	96%
4				Silica supported 12-tungstophoric acid [27]	2 h	92%
5				Silica supported sulfuric acid [28]	1-2 h	90%
6				Silica supported perchloric acid ($HClO_4$- SiO_2) [29]	20 min	60-90%
7				Amberlyst-15 [30]	3.5 h	90%
8				Amberlyst A-21 $Yb(OPf)_3$ [30]	25 min	93-97%
9				FeAlP-550 amorphous mesoporous iron aluminophosphate [31]	45 min.	87-94%

Table 2. Catalytic study of various Lewis acids in the synthesis of 1,5 benzodiazepines.

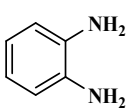
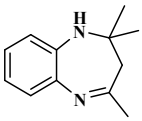
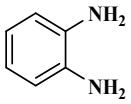
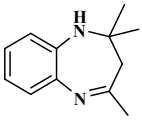
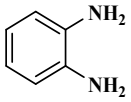
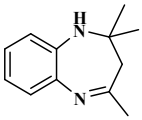
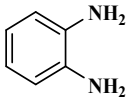
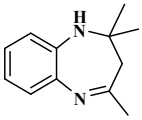
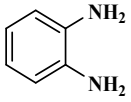
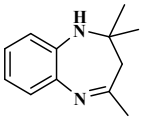
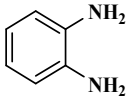
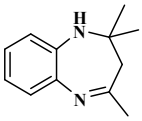
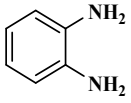
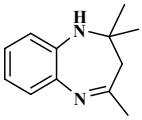
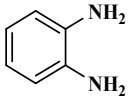
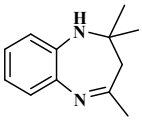
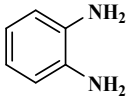
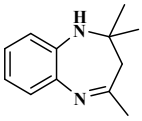
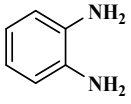
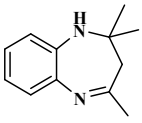
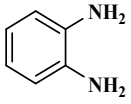
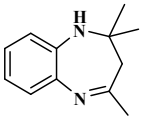
Entry	Diamine	Ketone	Product	Catalyst	Time	Yield (%)
1				$MgO/POCl_3$[33]	0.5 h	90%
2				$Yb(OTf)_3$ [34]	4 h	96%
3				[bbim]Br [35]	50 min.	93%
4				$Sc(OTF)_3$ [37]	3 min.	90%
5				I_2 [48]	5 min.	95%
6				$InCl_3$ [36]	5 h	91%
7				$InBr_3$ [36]	1.5 h	95%
8				$AgNO_3$ [39]	30 min.	84-95%
9				$YbCl_3$ [40]	15 h	85%
10				$LaCl_3.\ 7H_2O$ [41]	30 min	82-91%
11				$ZrCl_4$ [42]	30-180 min.	96%

Table 2. *(Continued).*

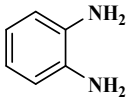
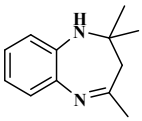
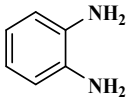
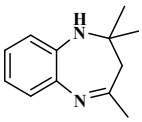
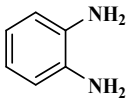
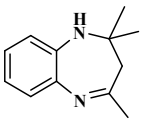
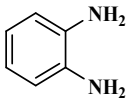
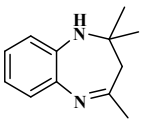
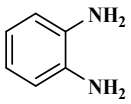
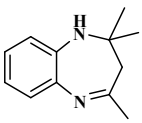
12				$Ga(OTF)_3$ [45]	20 h	87-94%
13				$MgBr_2$ [46]	60 min.	93-98%
14				$NaAuCl_4$. $2H_2O$[47]	60 min.	95%
15				$ZrOCl_2$. $8H_2O$ [49]	15 min.	80%
16				$SnCl_2$ [50]	40-60 min	92%

Table 3. Catalytic study of various organo acids in the synthesis of 1,5-benzodiazepines

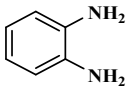
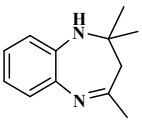
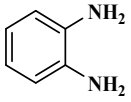
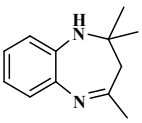
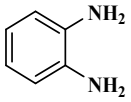
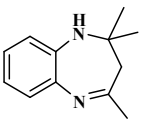
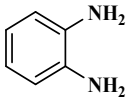
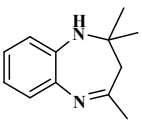
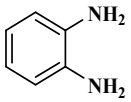
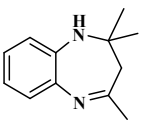
Entry	Diamine	Ketone	Product	Catalyst	Time	Yield (%)
1				Glacial acetic acid(MW) [52]	2-7 min	90-99%
2				Polyphosphoric acid (PPA) [55]	3 h	83%
3				Sulfamic acid [56]	24 h	83%
4				Benzoic acid[57]	24 h	80%
5				*p*-Nitrobenzoic acid [57]	7 h	90%

Table 3. *(Continued).*

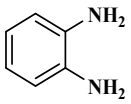
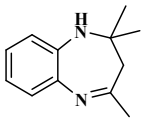
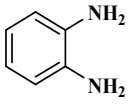
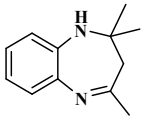
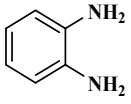
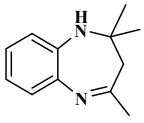
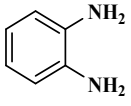
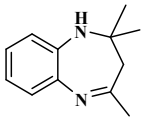
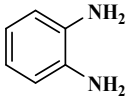
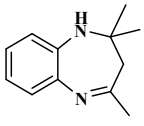
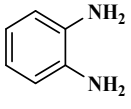
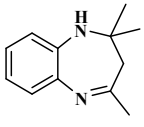
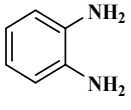
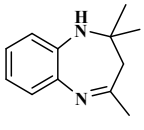
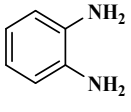
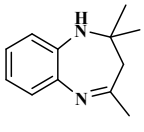
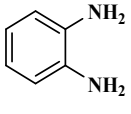
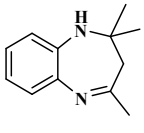
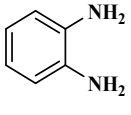
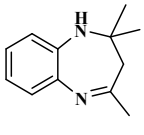
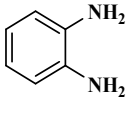
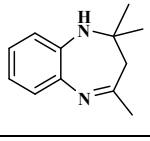
6				*m*-Bromobenzoic acid [57]	24 h	60%
7				Phenylacetic acid [57]	24 h	80%
8				Mandelic acid [57]	24 h	32%
9.				*p*-Toluene sulphonic acid [57]	72 h	N.R.
10				Cinnamic acid [57]	24 h	No reaction
11				Anthanilic acid[57]	24 h	83%
12				*o*-picolinic acid [57]	24 h	79%
13				Isonicotinic acid [57]	24 h	83%
14				Malonic acid [57]	24 h	85%
15				Adipic acid [57]	12 h	78%
16				Valaric acid [57]	24 h	40%

Table 3. *(Continued).*

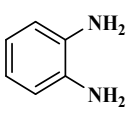
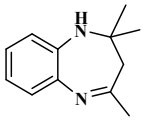
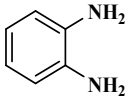
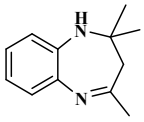
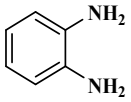
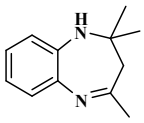
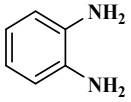
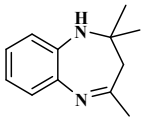
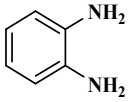
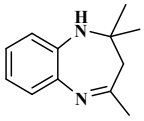
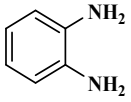
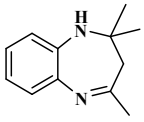
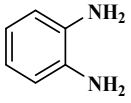
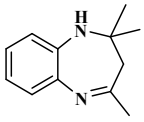
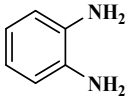
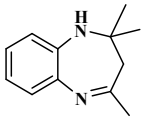
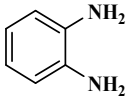
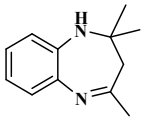
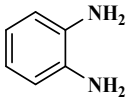
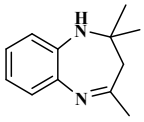
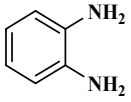
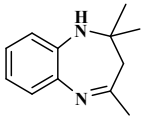
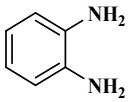
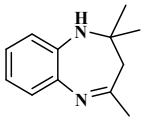
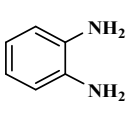
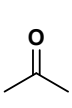
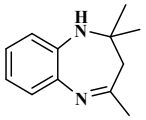
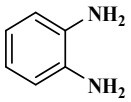
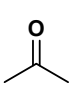
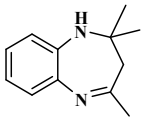
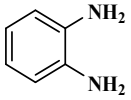
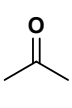
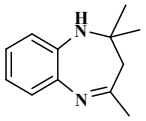
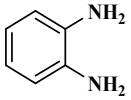
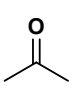
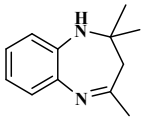
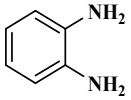
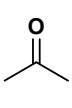
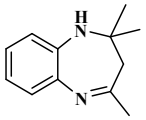
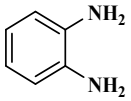
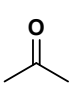
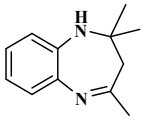
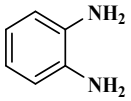
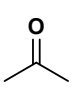
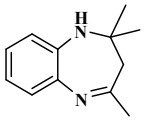
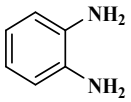
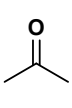
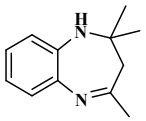
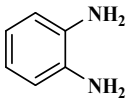
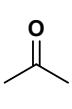
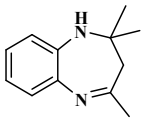
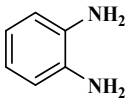
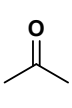
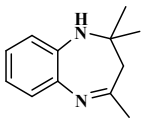
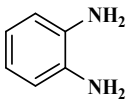
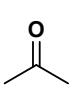
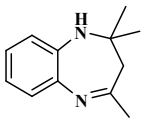
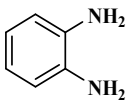
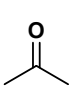
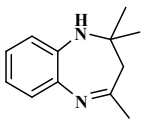
17				Citric acid [60]	12 h	88%
18				Iminodiacetic acid [57]	24 h	No Reaction
19				*p*-Anisic acid [57]	24 h	85%
20				Trimesic acid [57]	10 min.	97%
21				Sulfanilic acid [58]	40-60 min.	93-97%
22				Boric acid [59]	7-11 min.	82-95%
23				PABA [61]	24h	92%
24				Salicylic acid [62]	1h	94%
25				Tannic acid [63]	1h	92%
26				Phenyl bronic acid [64]	11-12 h	82-91%
27				Boron sulfonic acid [65]	30-40 min	85-99%
28				TFA [66]	12h	85-94%

Table 4. Catalytic study of selected miscellaneous acids in the synthesis of 1,5 benzodiazepines.

Entry	Diamine	Ketone	Product	Catalyst	Time	Yield (%)
1				SO_4^{2-}/ZrO_2 [69]	1 min.	90-99%
2				NBS [73]	24 h	83%
3				$H_{14}[NaP_5W_{30}O_{110}]$ [79]	60-120 min.	83%
4				SmI_2 [67]	2-5 h	80%
5				CH_2Cl_2(APTS) [78]	24 h	79%
6				TCT [87]	5.5 h	65-99%
7				PDTN-Silver complex [89]	Stirring at r.t.	87-94%
8				Bi (III) salts [91]	1 h	95%
9				H-MCM-22 [92]	2 h	92%
10				NaClO4 [94]	3.0 min	90 %
11				Argentinean bentonite [95]	1-3 h	86-90%
12				2-Methylpyridinium trifluoromethane sulfonate [98]	2 2 min	95 %

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