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REVIEW

Catalyst Supported Synthesis of 1,5-Benzodiazepines: A Review

Piyush Chahal✉ and Shweta Verma

ABSTRACT

1,5-Benzodiazepines are an eminent class of drugs of particular interest for advance discovery as they have been found active against different families of targets. This current review article covers all the different catalysts employed for the synthesis of 1,5-benzodiazepines accomplished since 2000.

KEYWORDS

Catalyst, Benzodiazepines.

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Author affiliations:

Faculty of Pharmacy, IFTM University, Moradabad-244 001, India

✉To whom correspondence to be addressed:

E-mail: jatpiyushchahal@gmail.com

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INTRODUCTION

Benzodiazepines are an important pharmacophore due to their pharmacotherapeutic properties and various pharmacopeial information. 1,5-Benzodiazepine nucleus is a privileged scaffold that is a core structure of medicinal drugs and has received great attention of medicinal research searching for new derivatives with enhanced pharmacological activities [1]. Benzodiazepine derivatives are also important compounds family with various biological properties. They have attributed to many pharmacological activities among which are tranquilizing, antiviral, anti-inflammatory, analgesic, antipyretic and anticonvulsant [2]. Benzodiazepines are categorized as either short, intermediate or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia, longer-acting benzodiazepines are recommended for the treatment of anxiety [3]. Out of which about five 1,5-benzodiazepines are in therapeutic use for their sedative, anxiolytics and anticonvulsant activities *viz.* clobazam, arfendazam, lofendazam, triflubazam and CP-1414S. Clobazam has been marketed as an anxiolytics since 1975 and as an anticonvulsant since 1984 [4]. Benzodiazepine adducts are also considered as important precursors in the synthesis of benzimidazole, pyrazole, isoxazole and quinoxaline derivatives. Some of the important medicinal drugs have been shown in Fig. 1.

Catalyst

Phosphonitrilic chloride acid: Sagar *et al.* [5] in their preliminarily investigation on model reaction of *o*-phenylenediamine and acetophenone found that reaction could be finished in 2 h under simple reaction condition in the presence of catalytic amount 2.5 mol % of phosphonitrilic chloride acid

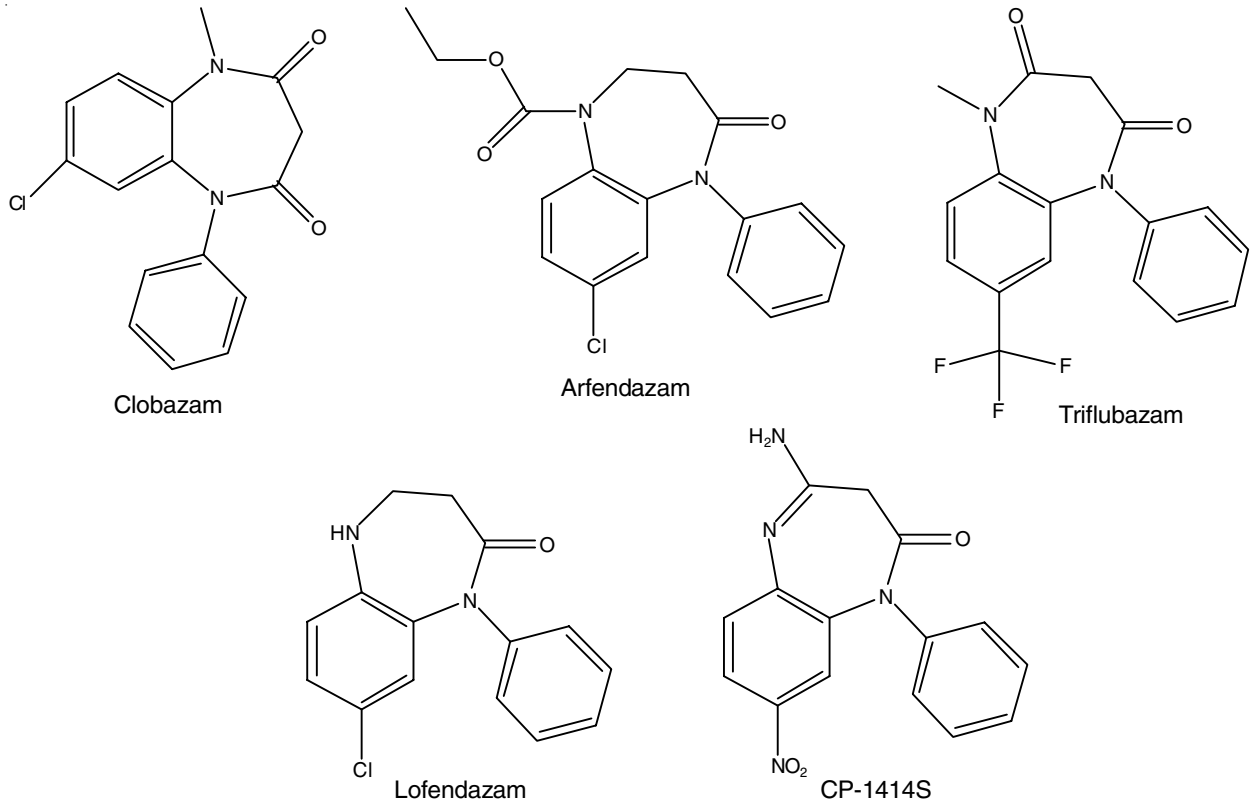

Fig. 1. Structures of important medicinal drugs containing 1,5-benzodiazepine nucleus

(PNT) and 3-4 drops of EtOH as solvent, which give desired 1,5-benzodiazepines products (about 80 % yields) (Fig. 2).

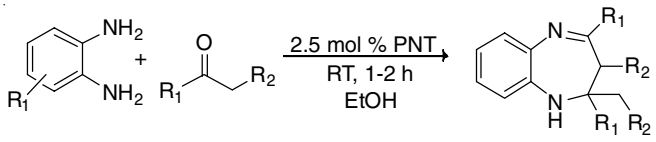

Fig. 2. Synthesis of 1,5-benzodiazepines using phosphonitrilic chloride acid as catalyst

Boron sulfonic acid: Sajjadifar and Rezayati [6] have reported an efficient synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and 1,2-diketones under solvent EtOH/H_2O conditions at room temperature using catalytic amount 10 %, 0.1 g of boron sulfonic acid [$B(HSO_4)_3$] as a catalyst. The reaction was carried out for 0.5 h and product was obtained with excellent 99 % yield (Fig. 3).

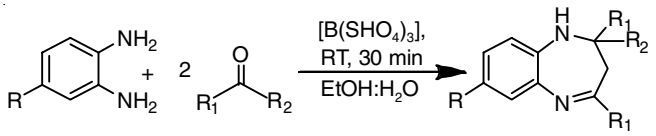

Fig. 3. Synthesis of 1,5-benzodiazepines using boron sulfonic acid as catalyst

Silicotungstic acid (STA): Kaur *et al.* [7] reported the synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with ketones by using catalytic amount 10 mol % of silicotungstic acid (STA) as a catalyst. The reaction was carried out for 20 min and product obtained with 89 % yield (Fig. 4).

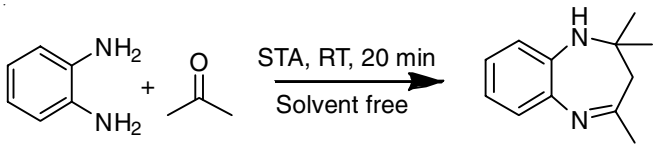

Fig. 4. Synthesis of 1,5-benzodiazepines using silicotungstic acid (STA) as catalyst

Chloroacetic acid: Sandhar and Singh [8] in their study repored a series of synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with different ketones and aliphatic acid using catalytic amount 10 mol % or 0.1 mmol of chloroacetic acid and the excellent results (94 % yields) were achieved within 1 h (Fig. 5).

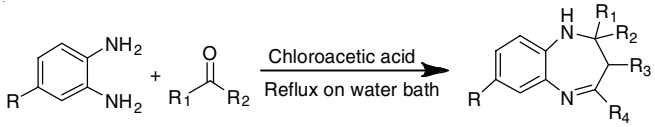

Fig. 5. Synthesis of 1,5-benzodiazepines using chloroacetic acid as catalyst

Silica sulfuric acid: Shushizadeh *et al.* [9] synthesized 1,5-benzodiazepine derivatives in the presence of catalytic amount 0.5 g of silica sulphuric acid, which was irradiated in a microwave oven under solvent free conditions. The reaction was carried out for 5-25 min and product was acquired from 78 to 95 % yield (Fig. 6).

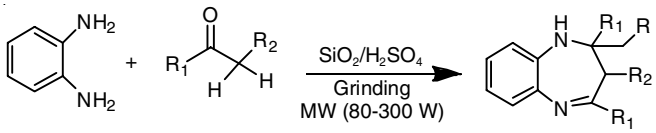

Fig. 6. Synthesis of 1,5-benzodiazepines using silica sulphuric acid as catalyst

Sodium perchlorate: Makone *et al.* [10] developed the green methodologies for the synthesis of heterocyclic compounds in an aqueous media. They reported the synthesis of 1,5-benzodiazepines using *o*-phenylenediamine, acetophenone and sodium perchlorate (2 mmol) in 5 mL of water, which was allowed to stir vigorously for 3 h at room temperature and product was obtained with 90 % yield (Fig. 7).

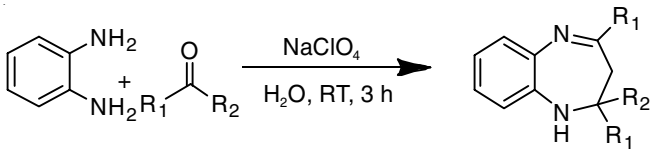

Fig. 7. Synthesis of 1,5-benzodiazepines using sodium perchlorate as catalyst

H-MCM-22: Tomar *et al.* [11] in their investigation reported a simple and versatile method for the synthesis of 1,5-benzodiazepines *via* condensation of *o*-phenylenediamine (OPDA) and ketones in the presence of catalytic amount of H-MCM-22 using acetonitrile as solvent at room temperature. The reaction was completed within 1-3 h with 87 % yield (Fig. 8).

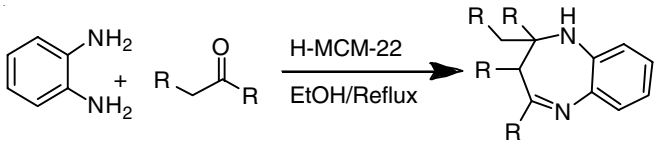

Fig. 8. Synthesis of 1,5-benzodiazepines using H-MCM-22 as catalyst

Tetrabutylammonium bromide (TBAB): Baseer and Khan [12] synthesized 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives in the presence of tetrabutylammonium bromide (TBAB) as a catalyst. The reaction was completed in short time with excellent 85-95 % yield (Fig. 9).

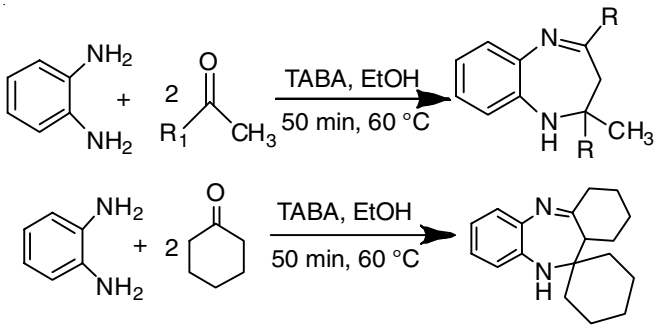

Fig. 9. Synthesis of 1,5-benzodiazepines using tetrabutylammonium bromide as catalyst

Citric acid: Baseer and Khan *et al.* [13] reported that 2,3-dihydro-1*H*-1,5-benzodiazepines were synthesized by reaction of *o*-phenylenediamine with ketones (acyclic/cyclic) in the presence of citric acid as catalyst at 60 °C under solvent free conditions. The reaction was carried out for 2 h and product was obtained with 77-85 % yield (Fig. 10).

Malonic acid: Langade [14] synthesized 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamine and ketones using malonic acid (10 mol %) as catalyst at 50 °C. The reaction was carried out for 20 min and product was obtained with 98 % yield (Fig. 11).

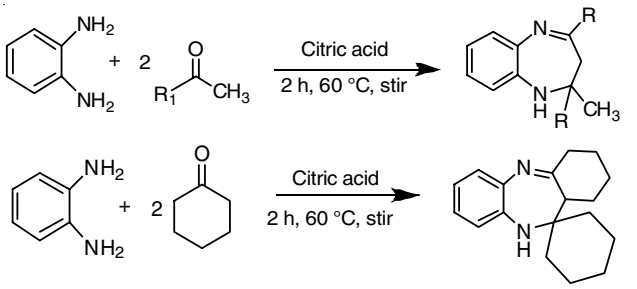

Fig. 10. Synthesis of 1,5-benzodiazepines using citric acid as catalyst

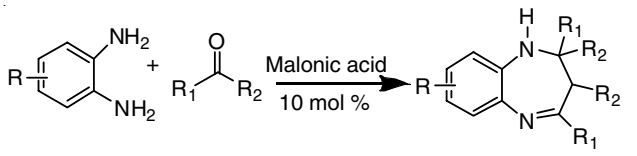

Fig. 11. Synthesis of 1,5-benzodiazepines using malonic acid as catalyst

Stannous chloride: Sharma *et al.* [15] synthesized several new 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives using *o*-phenylenediamine (OPDA) and ketones in the presence of anhydrous stannous chloride as catalyst at 80-85 °C under solvent free conditions. 1,5-Benzodiazepine derivatives were obtained in good yield (80 %) within 1 h (Fig. 12).

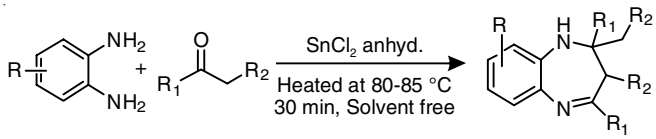

Fig. 12. Synthesis of 1,5-benzodiazepines using anhydrous stannous chloride as catalyst

Bismuth(III) salts: Chaskar *et al.* [16] reported the syntheses of 1,5-benzodiazepine derivatives by the condensation reactions of *o*-phenylenediamine and ketones by using catalytic amount 0.002 mol of bismuth(III) salts in ionic liquid (2 mL) at room temperature for 1 h. After the completion of reaction, 1,5-benzodiazepines yielded an excellent amount of 95 % (Fig. 13).

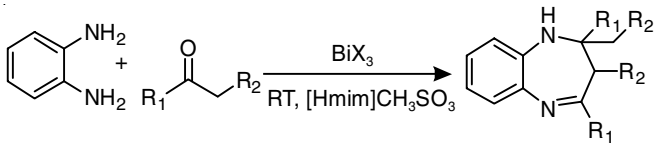

Fig. 13. Synthesis of 1,5-benzodiazepines using bismuth(III) salts in ionic liquid as catalyst

Sodium tetrachloroaurate(III) dihydrate: Shi *et al.* [17] reported the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and ketones using catalytic amount of 0.02 mmol sodium tetrachloroaurate(III) dihydrate and 5 mL ethanol as solvent at room temperature. The reaction was carried out for 5 h with excellent 95 % yield (Fig. 14).

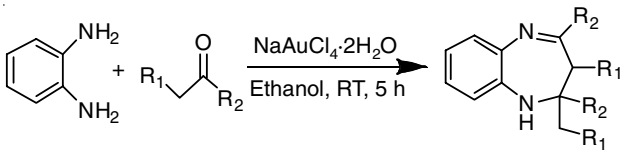

Fig. 14. Synthesis of 1,5-benzodiazepines using sodium tetrachloroaurate(III) dihydrate as catalyst

Gallium trichloride: Sandhu *et al.* [18] synthesized various 1,5-benzodiazepine derivatives using *o*-phenylenediamine and ketones in the presence of catalytic amount of gallium trichloride (5 mol %) in solvent free condition. The reaction was carried out for 0.5 h and products were obtained with excellent 94 % yields (Fig. 15).

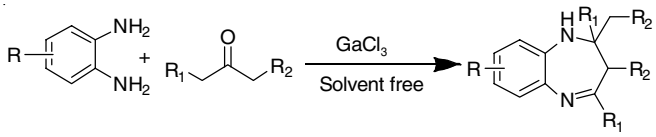

Fig. 15. Synthesis of 1,5-benzodiazepines using gallium trichloride as catalyst

Heteropoly acids: Heravi *et al.* [19] used used catalytic amount 1 mmol of heteropoly acids for the synthesis of 3*H*-1,5-benzodiazepines through the condensation of *o*-phenylenediamine and various 1,3-diketones in an appropriate solvent (10 mL). The reaction was refluxed out for 2 h and product was obtained with 85-97 % yield (Fig. 16).

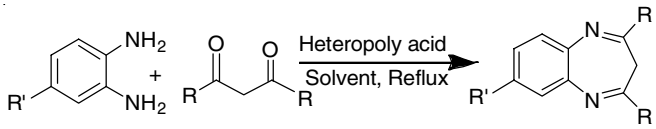

Fig. 16. Synthesis of 1,5-benzodiazepines using heteropoly acids as catalyst

Boric acid: Gholap and Tambe [20] reported the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from cyclocondensation of *o*-phenylenediamine and enolizable ketones using catalytic amount 10 mol % of boric acid as a green catalyst in water (3 mL) at room temperature for 0.5 h. After completion of reaction 2,3-dihydro-1*H*-1,5-benzodiazepines were obtained in excellent 99 % yield (Fig. 17).

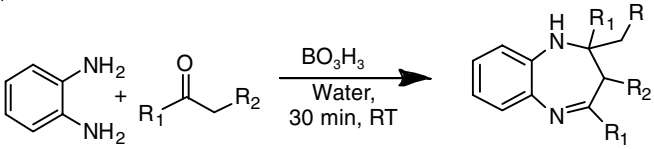

Fig. 17. Synthesis of 1,5-benzodiazepines using boric acid as catalyst

Ytterbium perfluorooctanesulfonate [Yb(Opf)$_3$]: Tao and Yi [21] synthesized 1,5-benzodiazepine derivatives by using a recyclable catalyst polymer-supported ytterbium perfluorooctanesulfonate and toluene as a solvent at 80 °C. After completion of reaction the yields were found in excellent 93-98 % amount (Fig. 18).

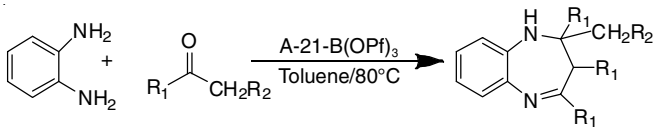

Fig. 18. Synthesis of 1,5-benzodiazepines using ytterbium perfluorooctanesulfonate as catalyst

Lanthanum chloride ($LaCl_3{\cdot}7H_2O$): Pandit *et al.* [22] synthesized 2,3-dihydro-1*H*-1,5-benzodiazepines in the presence of lanthanum chloride as a catalyst under solvent free conditions at 50 °C. The products were obtained in good 80-91 % yields (Fig. 19).

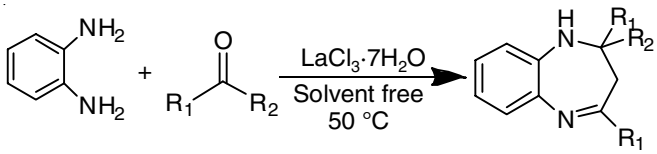

Fig. 19. Synthesis of 1,5-benzodiazepines using lanthanum chloride ($LaCl_3{\cdot}7H_2O$) as catalyst

***p*-Nitrobenzoic acid:** Varala *et al.* [23] synthesized 1,5-benzodiazepine derivatives by the condensation reactions of *o*-phenylenediamine and ketones using appropriate catalytic amount of *p*-nitrobenzoic acid as a catalyst under mild conditions using acetonitrile as solvent at ambient temperature and the isolated yields were found to be in the range 62-92 % (Fig. 20).

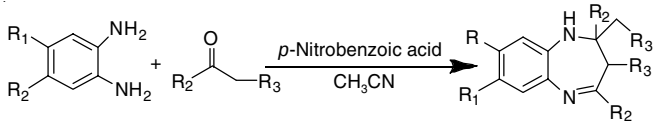

Fig. 20. Synthesis of 1,5-benzodiazepines using *p*-nitrobenzoic acid as catalyst

Cadmium chloride: Pasha and Ayashankara [24] synthesized 2,3-dihydro-1,5-benzodiazepines using acyclic/ cyclic & aromatic ketones and *o*-phenylenediamine in the presence of $CdCl_2$ at 80-85 °C under solvent free condition. The products were achieved with excellent 94 % yields within 10-20 min (Fig. 21).

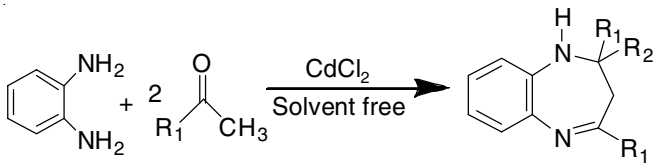

Fig. 21. Synthesis of 1,5-benzodiazepines using cadmium chloride as catalyst

Bromodimethyl sulfonium bromide: Das *et al.* [25] introduced an efficient solvent-free synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with ketones in the presence of specific catalytic amount of bromodimethyl sulfonium bromide at room temperature. The products were found with good to excellent yields (79-96 %) (Fig. 22).

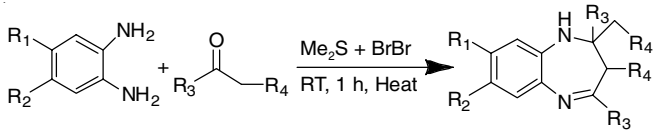

Fig. 22. Synthesis of 1,5-benzodiazepines using bromodimethyl sulfonium bromide as catalyst

***p*-Toulenesulfonic acid:** Pasha and Jayashankara [26] synthesized 1,5-benzodiazepine derivatives in the presence of *p*-toulenesulfonic acid as catalyst at 80-85 °C. After completion of reaction, the products were obtained with good yields (Fig. 23).

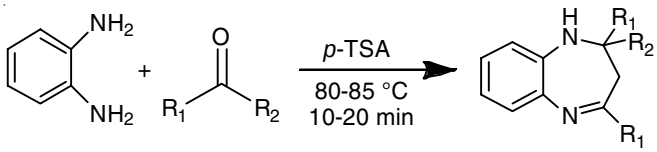

Fig. 23. Synthesis of 1,5-benzodiazepines using *p*-toulenesulfonic acid as catalyst

Silver nitrate: Chandra *et al.* [27] synthesized 2,3-dihydro-1*H*-1,5-benzodiazepines in the presence of silver nitrate under solvent free conditions. The reaction was carried out for 0.5 h and products were found with good to excellent yields (84-99 %) (Fig. 24).

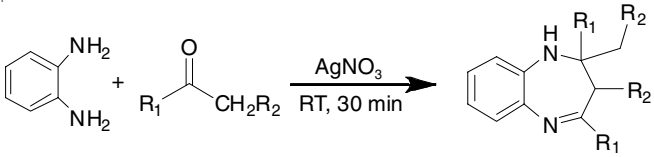

Fig. 24. Synthesis of 1,5-benzodiazepines using silver nitrate as catalyst

Polymer (PVP) supported ferric chloride: Chari and Syamasundar [28] synthesized 1,5-benzodiazepine derivatives using polymer (PVP) supported ferric chloride as catalyst in the condensation of *o*-phenylenediamine with ketones under solvent free conditions. The reaction proceeded efficiently under ambient conditions giving excellent yields (85-96 %) (Fig. 25).

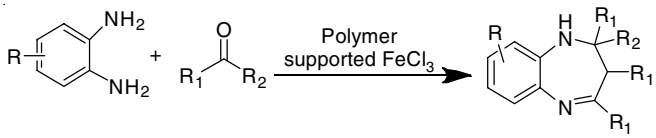

Fig. 25. Synthesis of 1,5-benzodiazepines using polymer (PVP) supported ferric chloride as catalyst

Solid super acid 'sulfated zirconia': Reddy and Sreekanth [29] reported a facile method for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones under solvent free conditions catalyzed by solid super acid sulfated zirconia. The reaction was carried out for 2-3 h and product obtained with 92 % yield (Fig. 26).

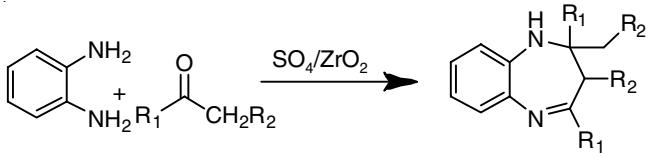

Fig. 26. Synthesis of 1,5-benzodiazepines using solid super acid sulfated zirconia as catalyst

Acetic acid: Stephanatou *et al.* [30] synthesized 2,3-dihydro-1*H*-1,5-benzodiazepines with *o*-phenylenediamine, ketones in solvent free conditions in the presence of a catalytic amount of acetic acid under microwave irradiation. After completion of reaction, the products were obtained with excellent yields (90-99 %) (Fig. 27).

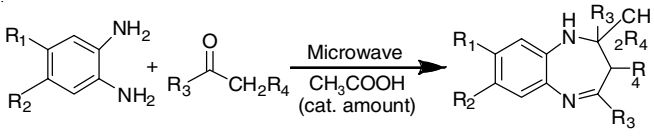

Fig. 27. Synthesis of 1,5-benzodiazepines using acetic acid as catalyst

Ytterbium triflate [Yb(OTf)$_3$]: Curini *et al.* [31] synthesized 2,3-dihydro-1*H*-1,5-benzodiazepines by condensation of *o*-phenylenediamine with ketones in the presence of Yb(OTf)$_3$ as catalyst in solvent-free conditions. After completion of reaction, the products were obtained in a very good yields (88-99 %) (Fig. 28).

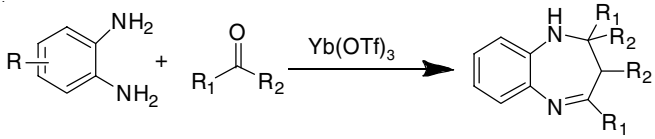

Fig. 28. Synthesis of 1,5-benzodiazepines using ytterbium triflate [Yb(OTf)$_3$] as catalyst

Samarium diiodide: Zhang *et al.* [32] demonstrated a new approach for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by using samarium diiodide as catalyst under mild and neutral conditions. The products were obtained in good yields (58-87 %) (Fig. 29).

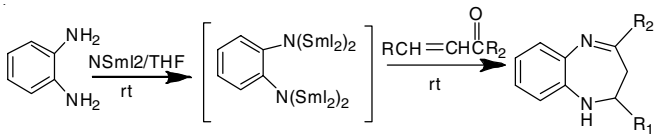

Fig. 29. Synthesis of 1,5-benzodiazepines using samarium diiodide as catalyst

Sulfated MCM-41: Vadival *et al.* [33] observed in their investigation that the condensation of *o*-phenylenediamine with aromatic ketones using catalytic amount 30 mol % of sulfuric acid loaded MCM-41 as a catalyst and 10 mL ethanol as solvent. The reaction mixture was refluxed was carried out for 4-5 h which provide good yield (~ 84-90 %) (Fig. 30).

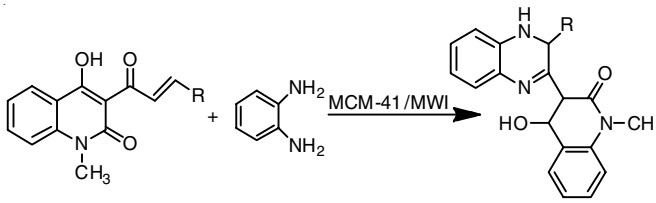

Fig. 30. Synthesis of 1,5-benzodiazepines using sulfuric acid loaded MCM-41 as catalyst

Conclusion

1,5-Benzodiazepine derivatives have received a great consideration in the field of medicinal chemistry. The various catalysts are employed for the synthesis of these compounds is found to be efficient providing green environment and excellent yield. The catalytic efficiency of boric acid, citric acid and chloro-acetic acid were found to be promising in lieu of green chemistry. The research has been continued in this field as this moiety proved to be highly efficacious in the treatment of various diseases and proved to be efficient for the synthesis of various scaffolds. This review aimed to focus on the different catalysts and strategies involved in the synthesis of this important pharmacophore.

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