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1,5-BENZODIAZEPINE: A VERSATILE PHARMACOPHORE

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ABSTRACT

Diazepines are an eminent class of drugs owing to their psychotherapeutic activities. Among these, 1,5-benzodiazepines are regarded as privileged structures due to their clinical importance and commercial success. Although immense work has been carried out on the benzodiazepine nucleus, it continues to receive a great deal of attention. Due to their vast range of biological properties the benzodiazepine nucleus has fascinated many investigators to synthesize and screen the analogues for all possible activities through all possible routes. This current review article mainly covers the various routes of synthesis utilized, the numerous solvents employed, catalysts used and the different pharmacological activities exhibited by 1,5-benzodiazepine derivatives. This review encompasses the research work that has been accomplished since the past decade.

KEYWORDS: 1,5-Benzodiazepines, o-Phenylenediamines, Synthesis, Catalyst, Diazepines

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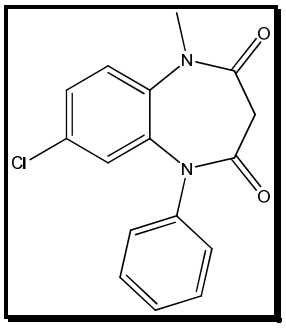
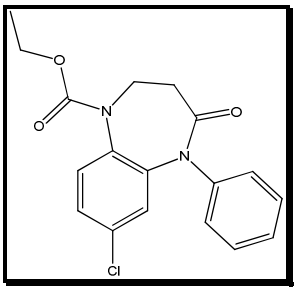
INTRODUCTION

Benzodiazepines are an important class of nitrogen containing heterocyclic compounds acting mainly on the central nervous system. They have attracted much attention in the field of medicine and pharmaceuticals due to their broad spectrum of biological activities. Immense research has been done on the benzodiazepine nucleus. A lot of work has been carried out to synthesize and screen its analogues for all possible activities due to its wide range of pharmacological activities.Recently 1,5-benzodiazepines have attained huge clinical importance and commercial success. It has proved to be a very versatile moiety as various derivatives of benzodiazepines have shown various activities like anticonvulsant, anti-anxiety, analgesic, sedative, antidepressant and hypnotic activities.[1,2] They have also been used in treatment of viral diseases[3,4], cardiovascular disorders[5] and as cholecystokinin (CCK) receptor antagonists.[6,7]The 1,5-benzodiazepine scaffold is extremely versatile and has featured in a number of clinically used drugs. Out of which about five 1,5-benzodiazepines are in therapeutic use for their sedative, anxiolytic and anticonvulsant activities viz. clobazam, arfendazam, lofendazam, triflubazam and CP-1414S.Clobazam has been marketed as an anxiolytic since 1975 and as an anticonvulsant since 1984.[8] It is marketed under the brand names frisium, urbanol and onfi. Clobazam has proved useful in the treatment of epilepsy, anxiety and also as a short term adjunctive agent in schizophrenia and other psychotic disorders to manage anxiety or agitation.

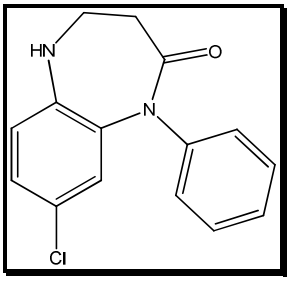


Clobazam

Arfendazam has sedative and anxiolytic effects. It produces muscle relaxant effects at very high doses.[9,10] It is closely related to clobazam and produces an active metabolite lofendazam, which is thought to be responsible for part of its effects.

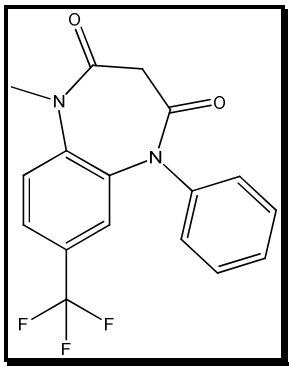


Arfendazam

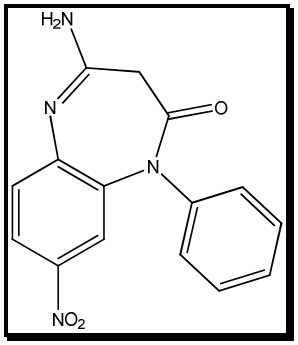


Lofendazam

Triflubazam and CP-1414S are closely related to clobazam. Triflubazam has sedative and anxiolytic effects.[11,12] CP-1414S is an experimental drug and shows primarily anxiolytic and anticonvulsant effects. Its potency is roughly equal to that of clobazam, but with more pronounced sedation.[13]



Triflubazam



CP-1414S

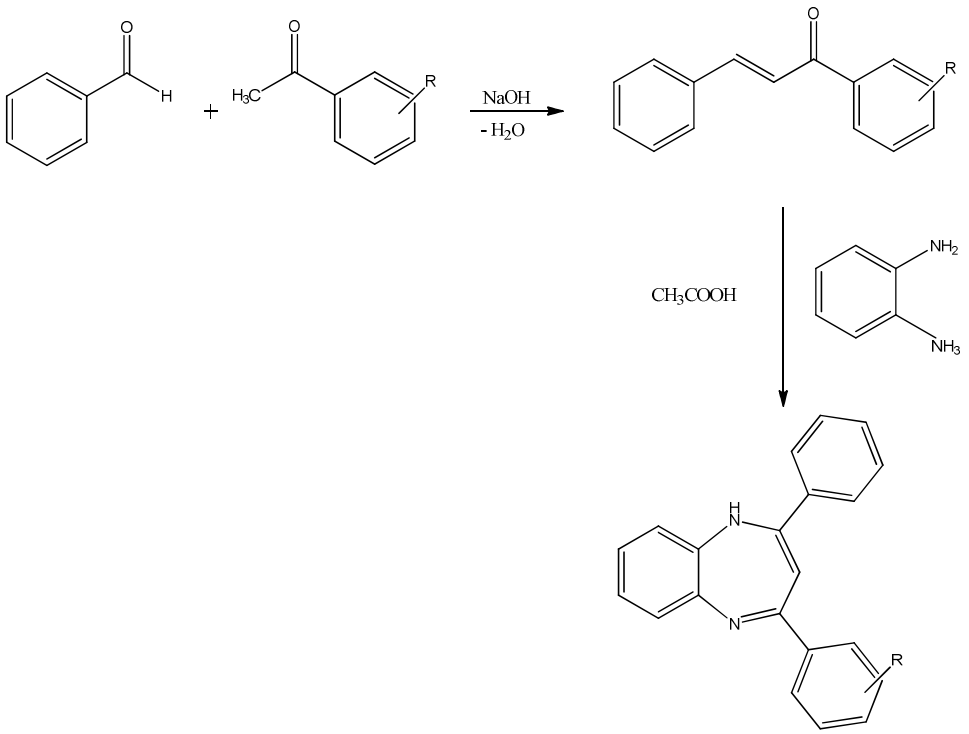
The present article is a review of most of the recent work that has been accomplished on the 1,5-benzodiazepine nucleus since the past decade based on the various routes of synthesis utilized, the numerous solvents employed, catalysts used and the different pharmacological activities exhibited by 1,5-benzodiazepine derivatives.

ROUTES OF SYNTHESIS EMPLOYED

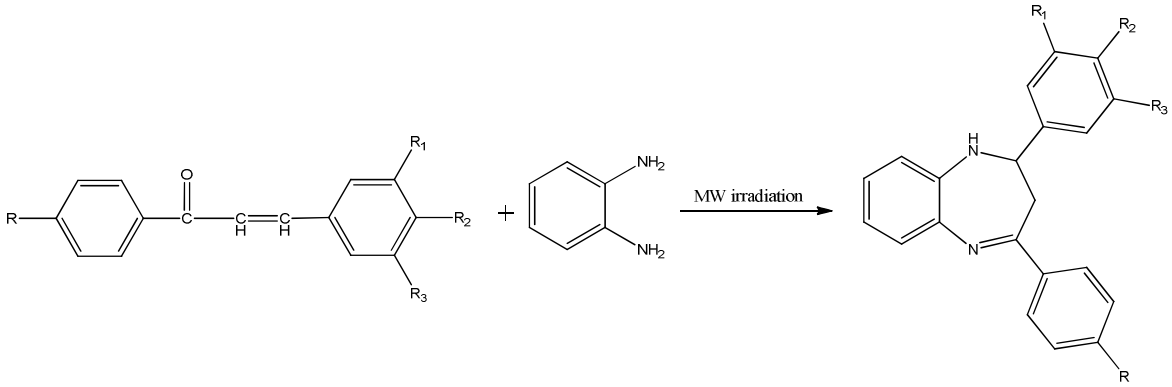
Investigators have synthesized 1,5-benzodiazepine derivatives through different routes of synthesis using various starting materials like α,β-unsaturated compounds, ketones, β-diketones, β-ketoesters, triazines, coumarins, etc. Various routes used have been described as follows.

From chalcones

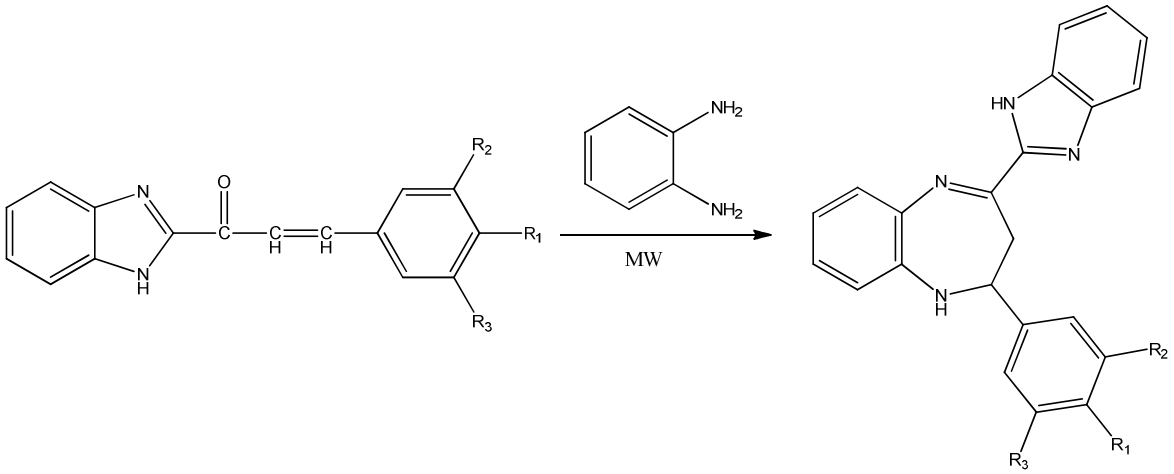
Bhatia et al.[14] carried out synthesis of 2,4-disubstituted-1,5-benzodiazepines from chalcones. The yields of the products were good (70-88%)



Sharma N et al.[15] synthesized a new series of 2,4-disubstituted-2,3-dihydro substituted-1,5-benzodiazepine derivatives from various substituted chalcones under solvent free microwave irradiation.

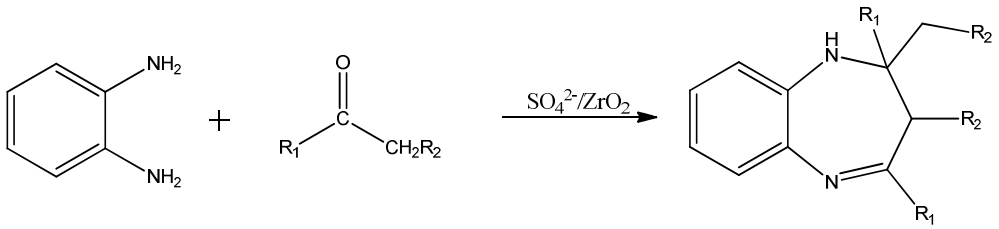


Srivastava YK et al.[16] synthesized some novel benzimidazole assembled 1,5-benzodiazepine derivatives from substituted chalcones.

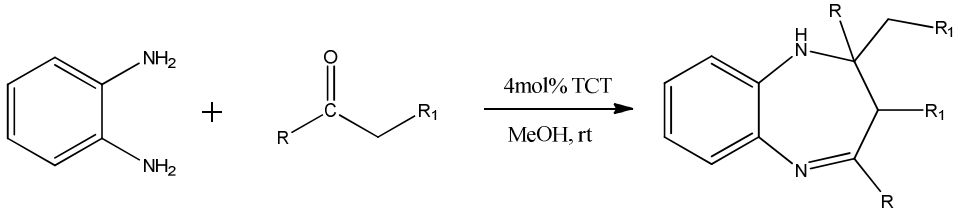


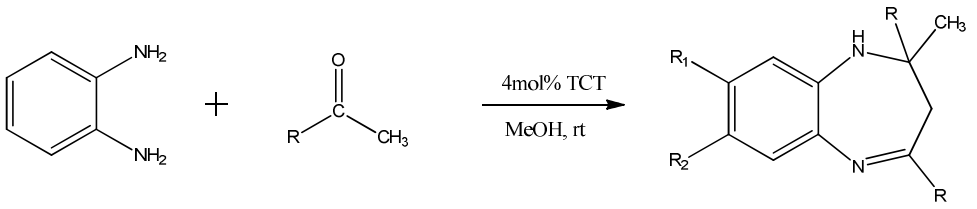
From ketones

Reddy BM et al.[17] carried out synthesis of 2,3-dihydro-1H-1,5-benzodiazepines from various ketones in the presence of a versatile solid superacid catalyst 'sulfated zirconia' under solvent free conditions. The yields obtained were good to excellent (80-96%).



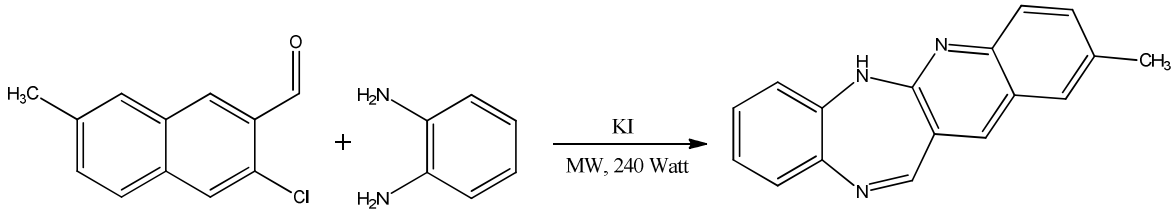
Kuo CW et al.[18] synthesized 1,5-benzodiazepine derivatives from enolizable ketones by using 2,4,6-trichloro-1,3,5-triazine as a catalyst. The products were obtained in excellent yields through simple and mild reaction conditions.





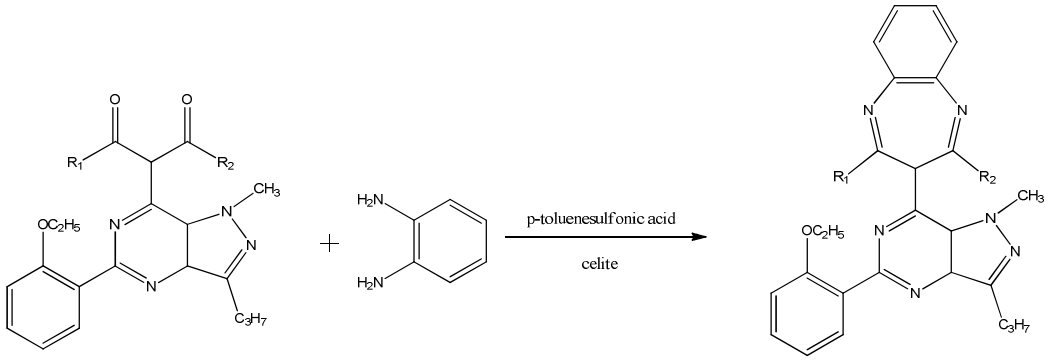
From quinoline carbaldehyde

Basavaraju B et al.[19] synthesized transition metal complexes of methylquinolino [3,2-b] [1,5]benzodiazepine from 2-chloro-6-methylquinoline-3-carbaldehyde.

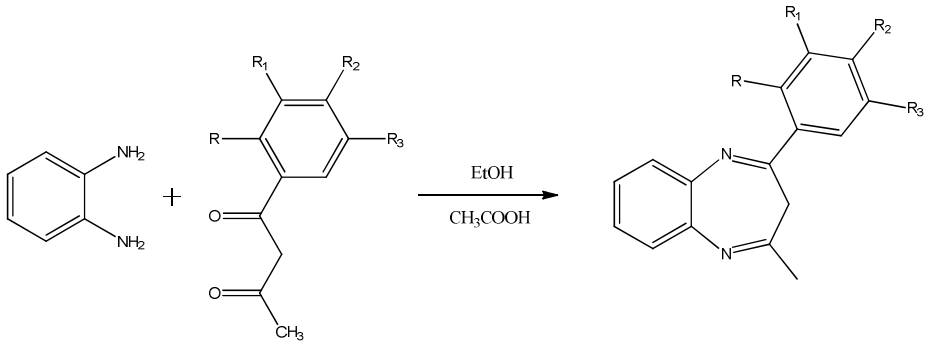


From β-diketones/β-ketoesters

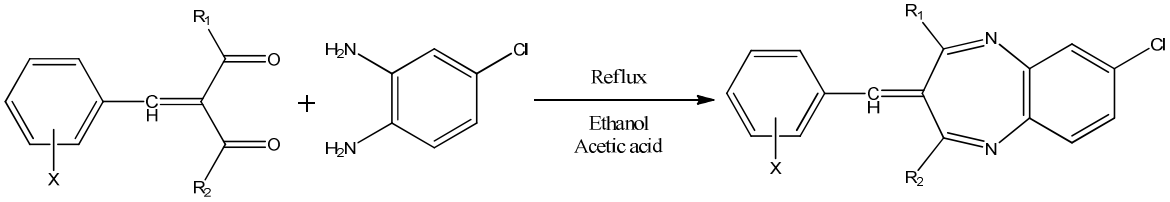
Kumar R et al.[20] synthesized 3H-1,5-benzodiazepine derivatives from β-diketones/β-ketoesters by using p-toluenesulfonic acid as catalyst.



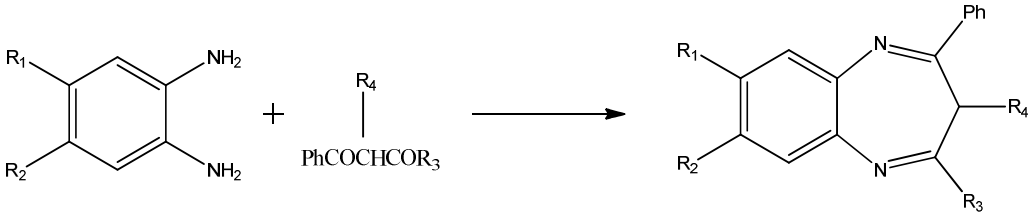
Vibhute A et al.[21] synthesized a series of 2-methyl-4-(substituted phenyl)-1,5-benzodiazepine derivatives from β-diketones.



Pathak VN et al.[22] synthesized a series of 3H-1,5-benzodiazepine derivatives from 2-arylidene-1,3-diketones and 4-chloro-1,2-phenylenediamine.



Tsoleridis CA et al.[23] carried out a facile synthesis of 4-phenyl-1H-1,5-benzodiazepines from o-phenylenediamines and 1,3-diketones in the presence of a catalytic amount of acetic acid has been achieved, in excellent yields, under microwave irradiation.

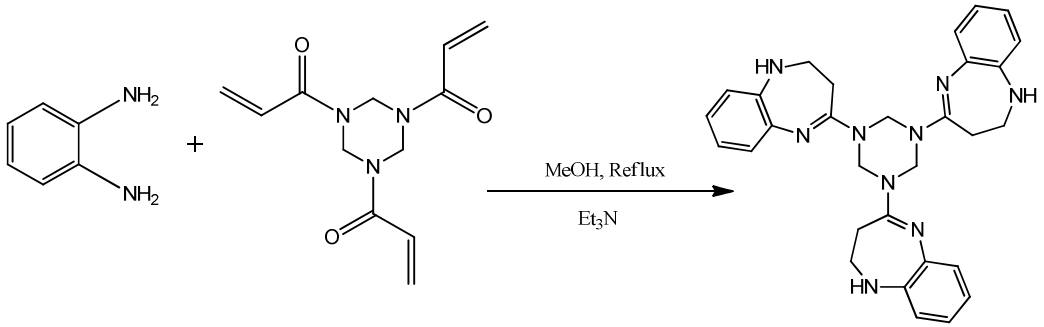


From β-ketoesters

Murai K et al.[24] demonstrated a novel one-pot three-component reaction of aromatic aldehydes, 1,2-phenylenediamine and β-ketoesters, which efficiently produced 1,5-benzodiazepine derivatives.

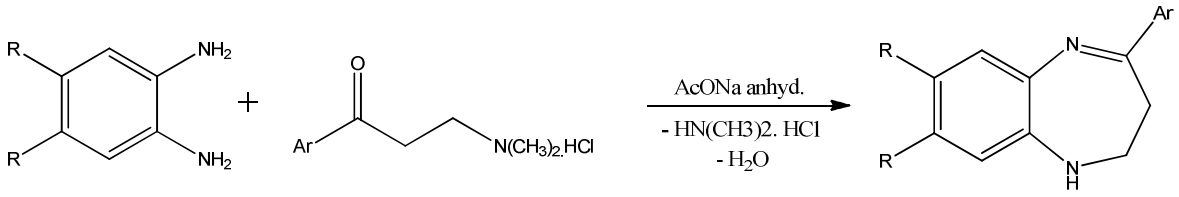
From triazine

Insuasty B et al.[25] synthesized a new 2,3-dihydro-1*H*-1,5-benzodiazepine derivative by reaction of o-phenylene diamine and trazine.



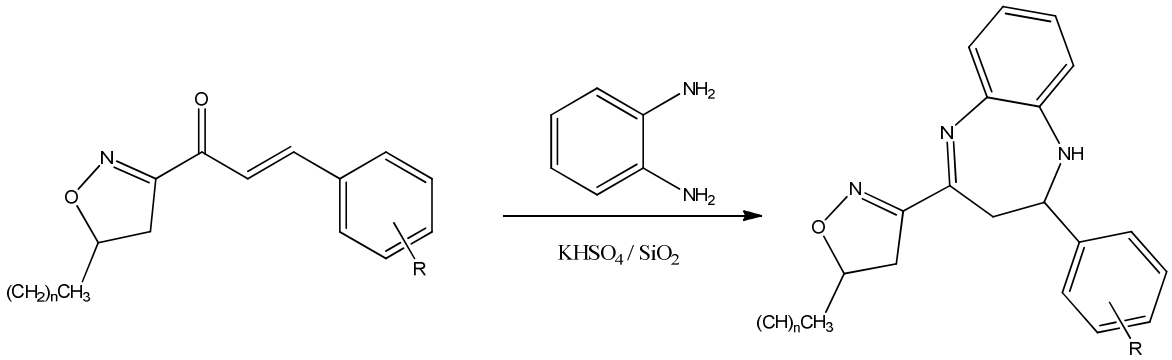
From β-aminoketones

Roman G et al.[26] synthesized 2,3-dihydro-1,5-benzodiazepines by base catalysed cyclocondensation of β-aminoketones.



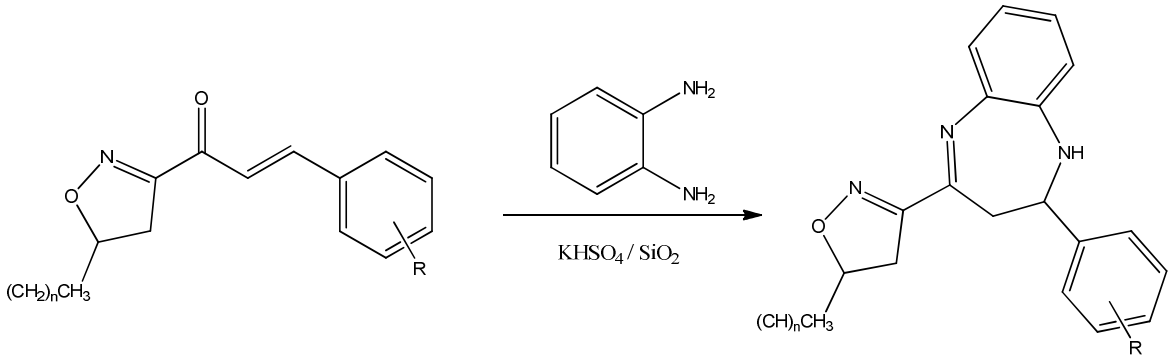
From isoxazole

Kapoor KK et al.[27] synthesized a series of novel 2,3-dihydro-1H-1,5-benzodiazepines from isoxazole derivatives and o-phenylenediamine, under solvent free conditions.



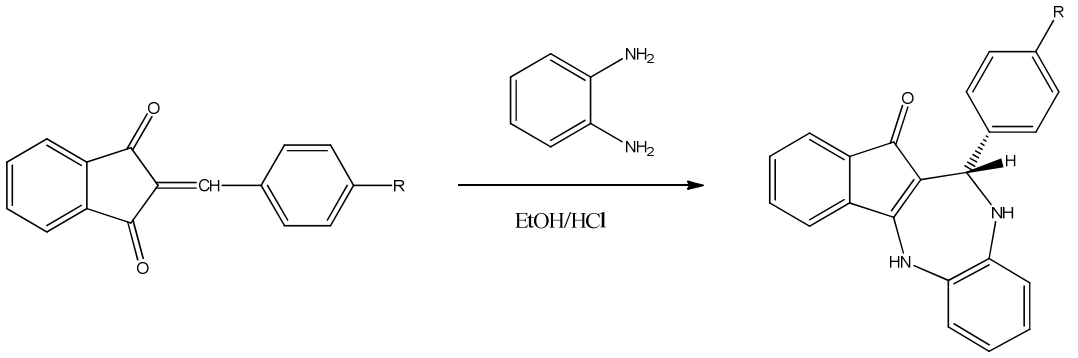
From coumarins

Kusanur RA et al.[28] synthesized spiro[indolo-1,5-benzodiazepines] from acetyl coumarins.



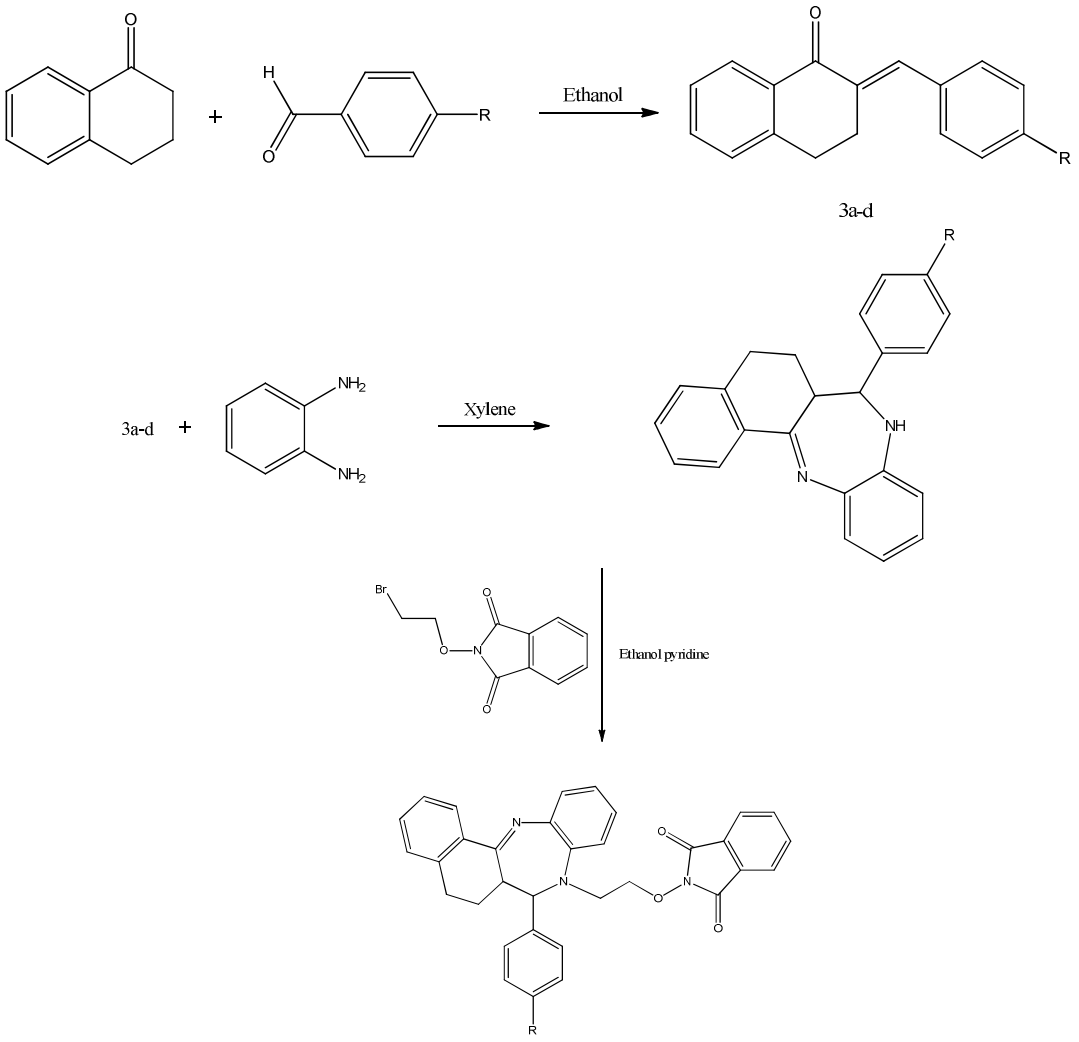
From indane diones

Aggarwal P et al.[29] synthesized some novel 1,5-benzodiazepin-7-ones from corresponding indane-1,3-diones in excellent yields.



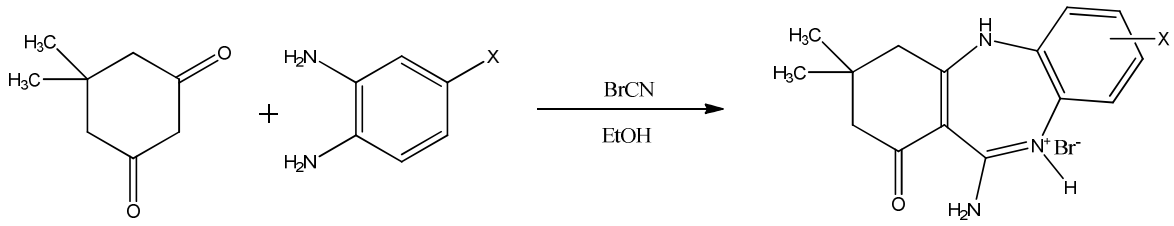
From α-tetralone

Sharma S et al.[30] synthesized some ethoxypthalimide derivatives of tetrahydro-naphtho[1,2-e][1,5]benzodiazepine by using α-tetralone and 4-substituted benzaldehyde as starting materials.



From dimedone

Nedjar Kolli et al.[31] demonstrated high yielding synthesis off a series of amino-1,5-benzodiazepine derivatives bearing a dimedone moiety.

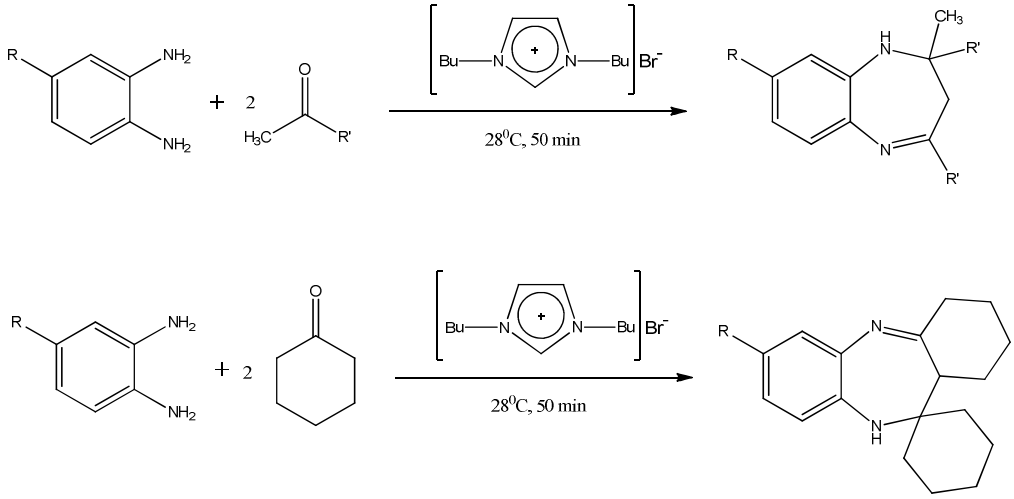


VARIOUS SOLVENTS USED

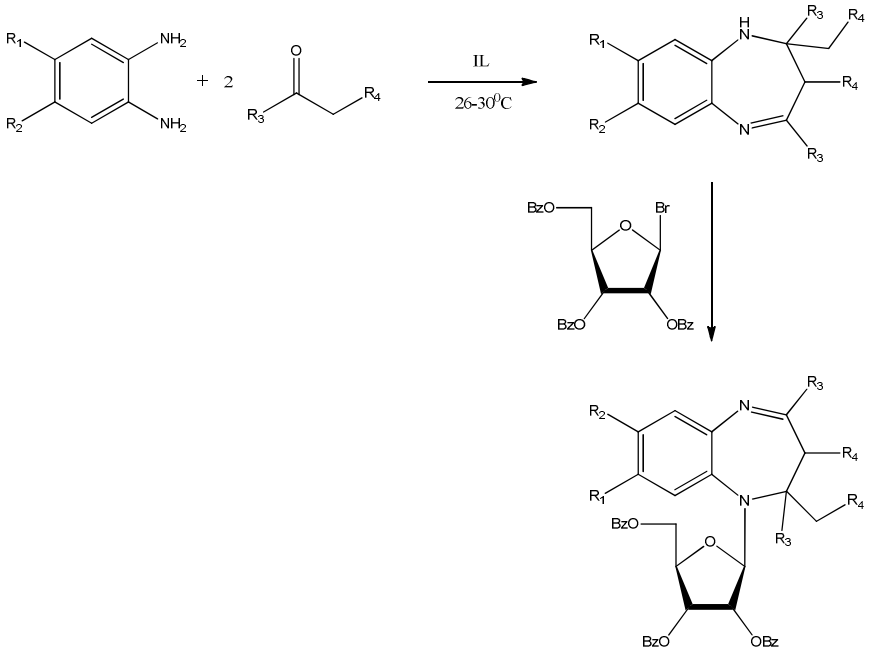
Apart from the commonly used solvents i.e. alcohols, the following solvents have also been used in the synthesis of 1,5-benzodiazepines.

Ionic liquids

Srinivasan KV et al.[32] used ionic liquid 1,3-di-n-butylimidazolium bromide and afforded 1,5-benzodiazepines in excellent isolated yields in the absence of a catalyst at ambient temperature.

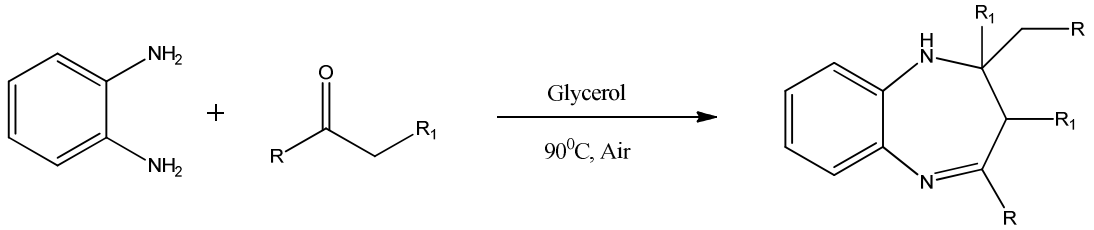


Yadav AK et al.[33] synthesized novel 1,5-benzodiazepine ribofuranosides by using various ionic liquids as catalyst at room temperature. The yields of the targeted compounds are excellent (72-90%).



Glycerol

Radatz CS et al.[34] have performed a catalyst-free synthesis of 1H-1,5-benzodiazepines by using glycerol as solvent, which can be easily re-utilized for further condensation reactions up to four times without lost of activity. This proved to be a simple and efficient method for obtaining the products in good yields.

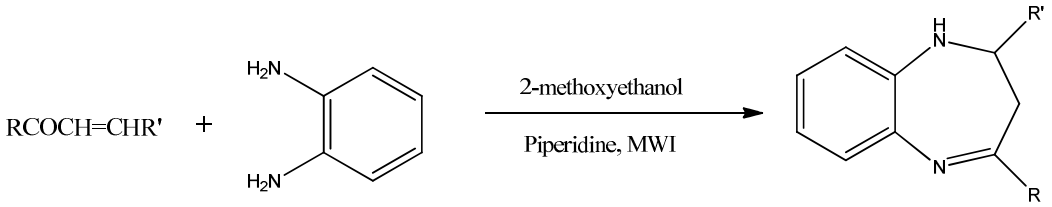


Acetonitrile

Varala R et al.[35] synthesized 1,5-benzodiazepine derivatives in good isolated yields (62-92%) under mild conditions using acetonitrile as solvent at ambient temperature in the presence of p-nitrobenzoic acid as catalyst.

2-methoxyethanol

Zangade S et al.[36] synthesized 1,5-benzodiazepines in the presence of 2-methoxyethanol as an alternative reaction solvent under microwave irradiation. The clean reaction conditions, easy work-up, time saving and higher yields are notable advantages of present method.

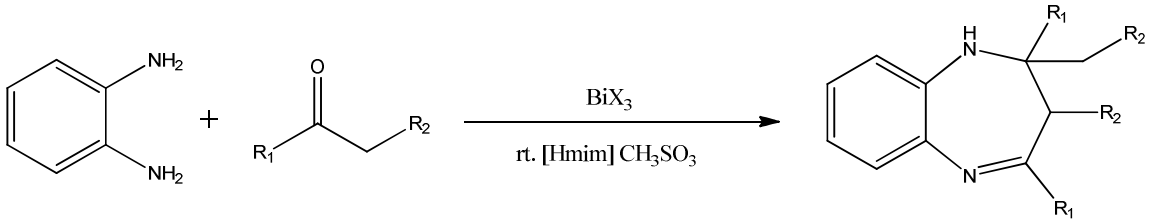


VARIETY OF DIFFERENT CATALYSTS USED

A large variety of different catalysts are employed for synthesizing 1,5-benzodiazepine derivatives. Most of the reactions utilizing the various catalysts are solvent free thus ensuring much more efficient and expeditious synthesis of the desired compounds. Reactions involving the numerous types of catalysts have been mentioned below.

Bismuth (III) salts

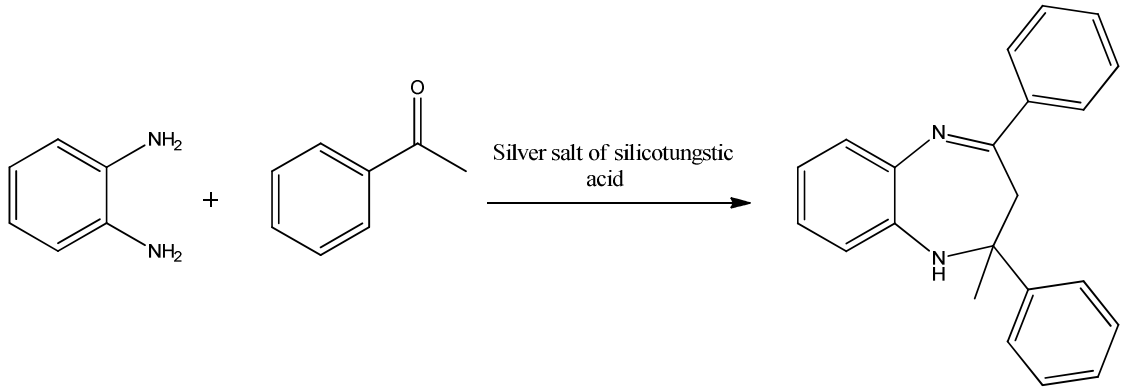
Chaskar A et al.[37] synthesized 1,5-benzodiazepine derivatives catalysed by Bismuth (III) salts under mild conditions in good to excellent yields.



Silver salt of silicotungstic acid

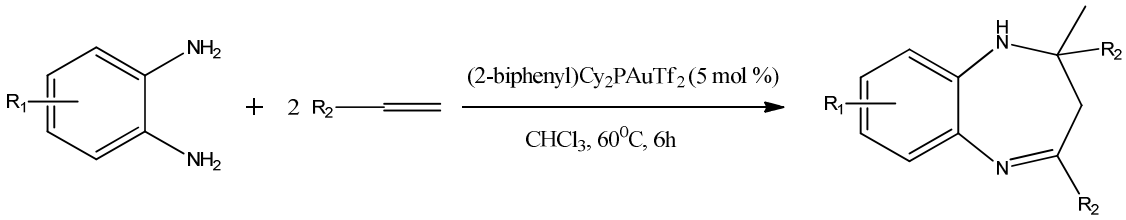
Jadhav AH and Kim H[38] synthesized 1,5-benzodiazepine derivatives by using prepared silver substituted silicotungstic acid (AgSTA) salt as a heterogeneous catalyst under solvent free

conditions at room temperature. This method was found to be a very convenient, fast, high yielding, and clean method for the synthesis of 1,5-benzodiazepine derivatives.



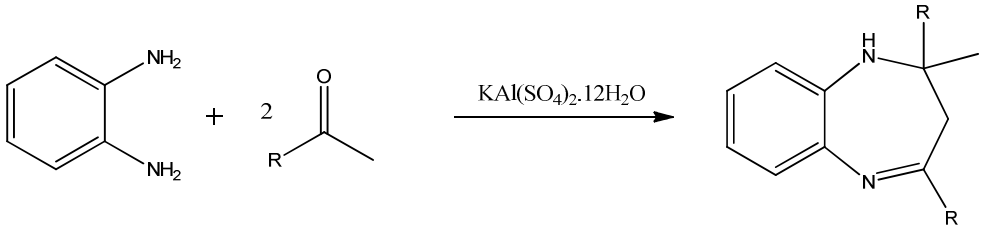
Gold (I) catalyst

Qian J et al.[39] carried out a unique gold(I) catalyzed highly atom-economic synthesis of 1,5-benzodiazepines directly from o-phenylenediamines and alkynes for the first time.



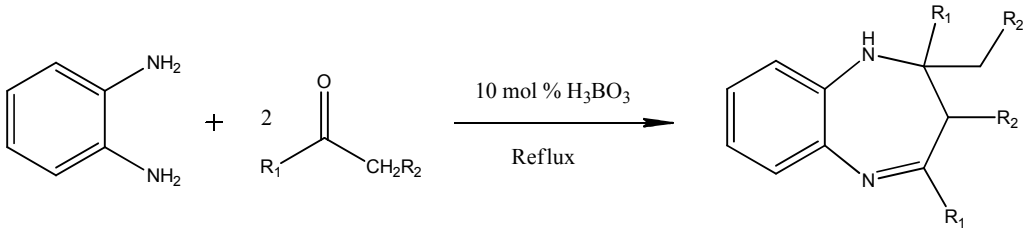
Alum

Kapoor K et al.[40] carried out an alum catalyzed one-pot solvent less synthesis of 1,5-benzodiazepines in good to excellent yields.



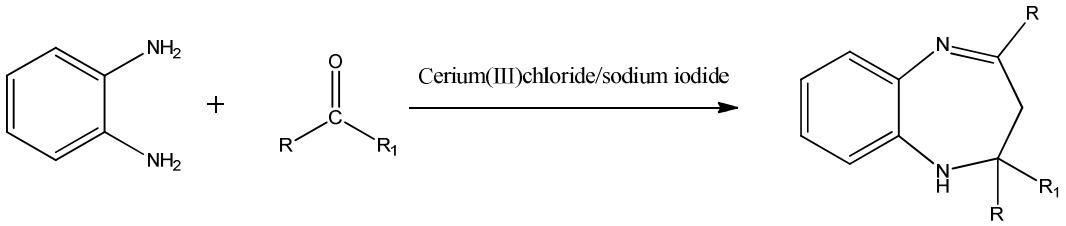
Boric acid

Wang C et al.[41] synthesized 1,5-benzodiazepine derivatives in the presence of boric acid as catalyst under mild conditions. This method is simple, environmentally benign and high yielding.



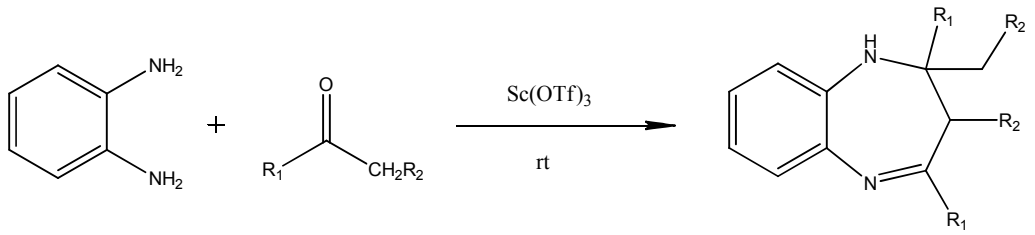
Cerium(III) chloride/ Sodium iodide

Gowravaram S et al.[42] carried out a novel and green synthesis of 2,3-dihydro-1H-1,5-benzodiazepines from o-phenylenediamines and ketones using cerium(III) chloride/sodium iodide supported on silica gel under mild and heterogeneous conditions. The reactions were carried out at room temperature without using any organic solvent.



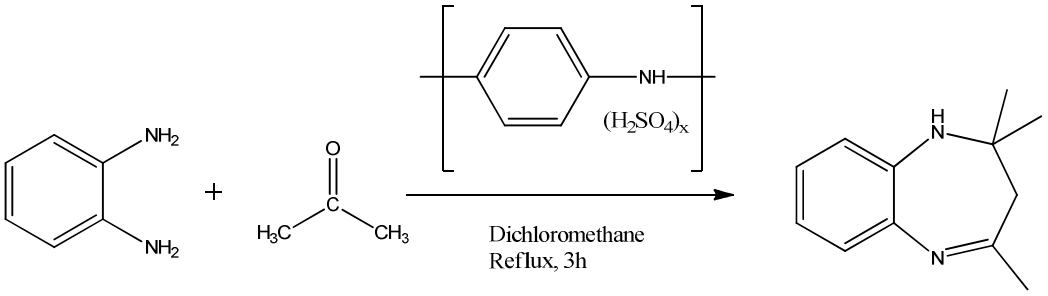
Scandium(III) triflate

De SK et al.[43] synthesized 2,3-Dihydro-1*H*-1,5-benzodiazepines in solvent-free conditions in excellent yield from *o*-phenylenediamines and ketones in the presence of a catalytic amount of $Sc(OTf)_3$. This method is a very easy, rapid, and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives.



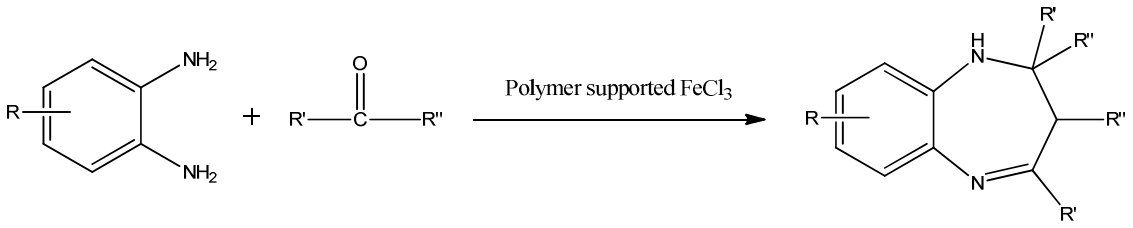
Polyaniline-sulfate salt

Palaniappan S et al.[44] used polyaniline-sulfate salt as an efficient and reusable catalyst for the synthesis of 1,5-benzodiazepines in excellent yields.



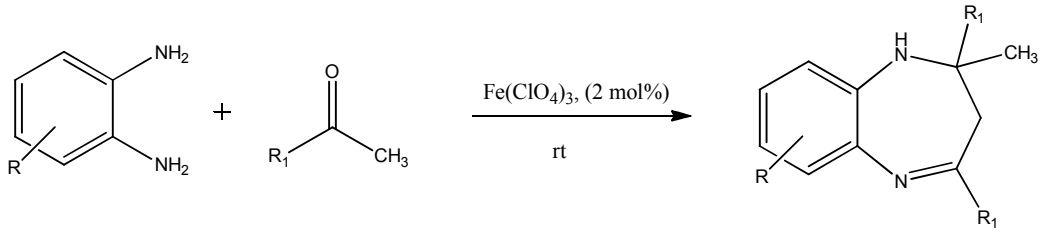
Polymer (PVP) supported ferric chloride

Chari MA et al.[45] used polymer (PVP) supported ferric chloride as catalyst in the condensation of o-phenylenediamines with ketones under solvent free conditions to afford the corresponding 1,5-benzodiazepine derivatives. The reaction proceeded efficiently under ambient conditions giving excellent yields (85–96%).



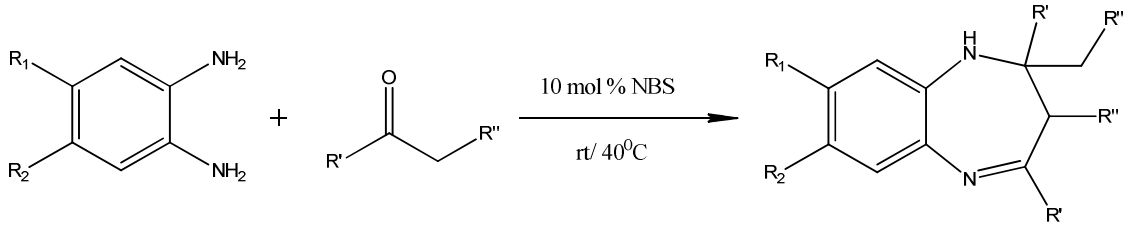
Ferric perchlorate

Heravi MM et al.[46] synthesized 2,3-dihydro-1H-1,5-benzodiazepines by the condensation of *o*-phenylendiamine and various ketones in the presence of $Fe(ClO_4)_3$.



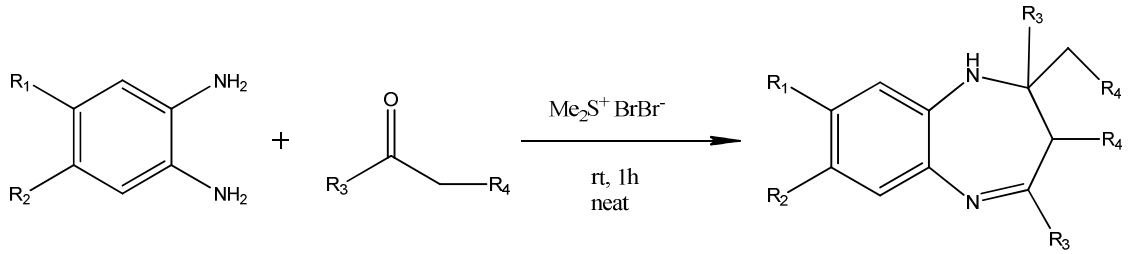
NBS

Yao C et al.[47] synthesized various biologically important 1,5-benzodiazepine derivatives in excellent yields using catalytic amounts of NBS.



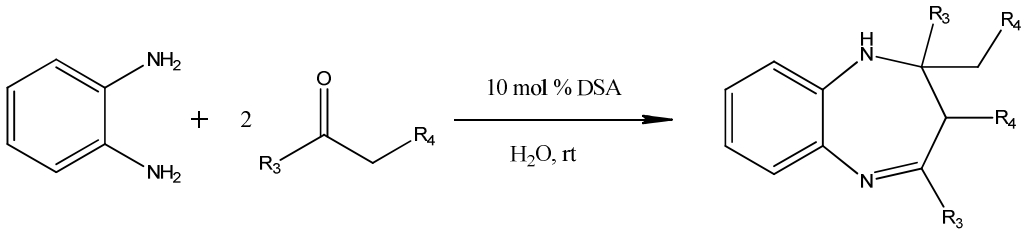
(Bromodimethyl) sulfonium bromide

Das B et al.[48] demonstrated an efficient solvent-free synthesis of 1,5-benzodiazepines by condensation of o-phenylenediamines with ketones in the presence of catalytic amount of (bromodimethyl) sulfonium bromide. The condensation occurred at room temperature and the products were formed in good to excellent yields (79 – 96%).



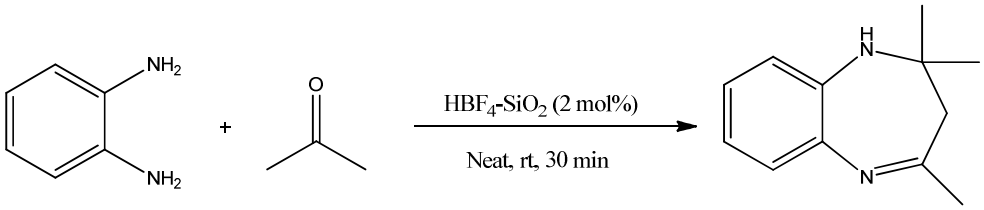
Dodecyl sulfonic acid

Sharma SD et al.[49] carried out a highly efficient and green method for the synthesis of 1,5-benzodiazepines by employing dodecyl sulfonic acid as an excellent surfactant-type Bronsted acid catalyst in aqueous media at room temperature.



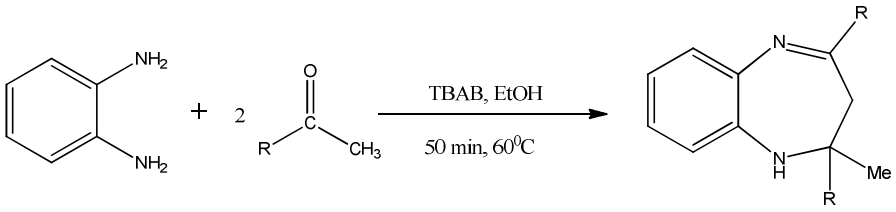
Silica supported fluoroboric acid

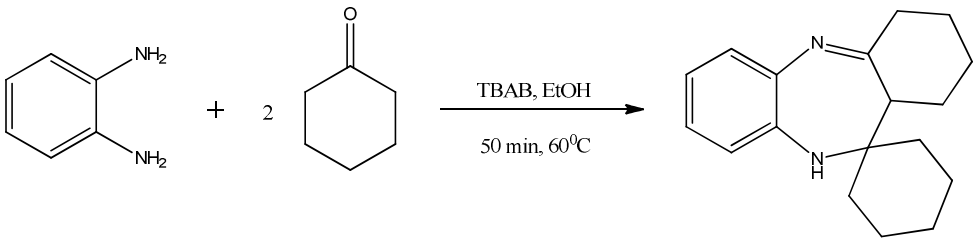
Bandgar BP et al.[50] carried out an efficient synthesis of 1,5-benzodiazepines from o-phenylenediamine and ketones under solvent-free conditions in the presence of HBF_4–SiO_2. High yield of the products with selectivity in short reaction time were obtained.



Tetra butyl ammonium bromide (TBAB)

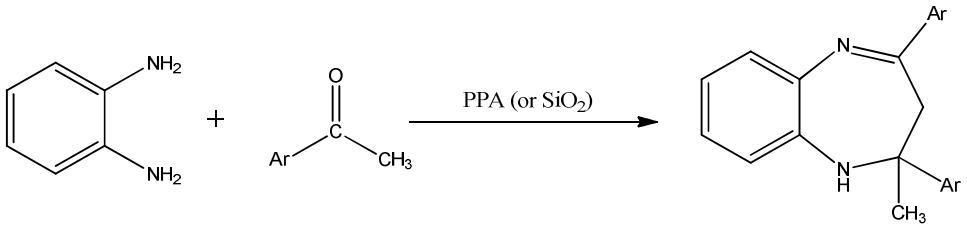
Baseer MA et al.[51] synthesized 2,3-dihydro-1H-1,5-benzodiazepine derivatives in the presence of tetra butyl ammonium bromide (TBAB) in short reaction time with excellent yield (85-95%).





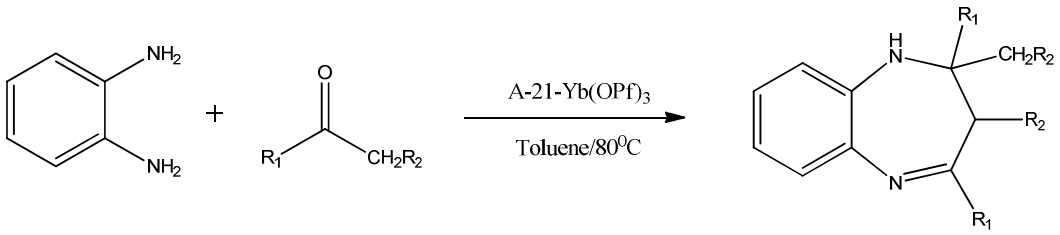
Polyphosphoric acid (PPA)

Jung D et al.[52] synthesized 1H-1,5-benzodiazepine derivatives from heterocyclic ketones in the presence of polyphosphoric acid as catalyst.



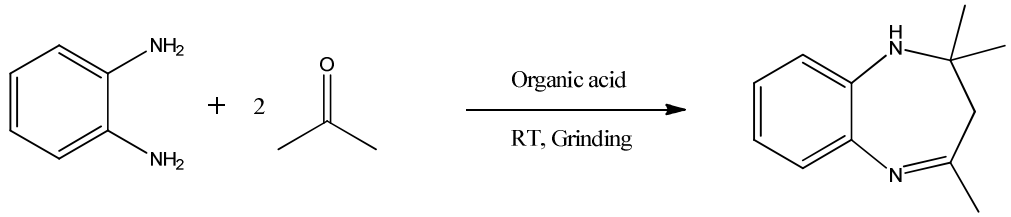
Ytterbium Perfluoroocatanesulfonate [Yb(OPf)$_3$]

Tao F et al.[53] used a recyclable catalyst polymer-supported Ytterbium perfluorooctanesulfonate for the synthesis of 1,5-benzodiazepine derivatives. The yields obtained were excellent (93-98%).



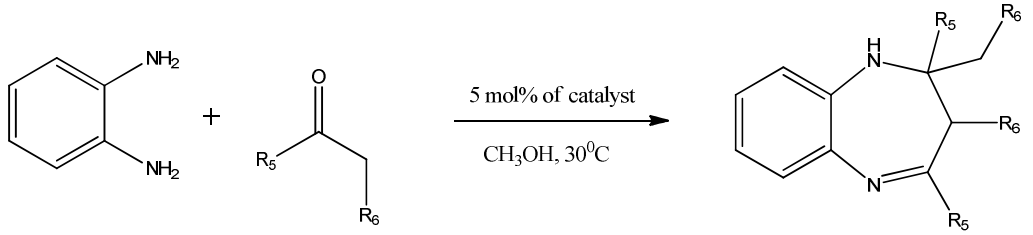
Organic acids

Das G et al.[54] carried out a one-pot reaction of o-phenylenediamines with acetone in the presence of catalytic amounts of different organic acids under solvent-free conditions afforded 1,5-benzodiazepine derivatives in excellent yields at room temperature.



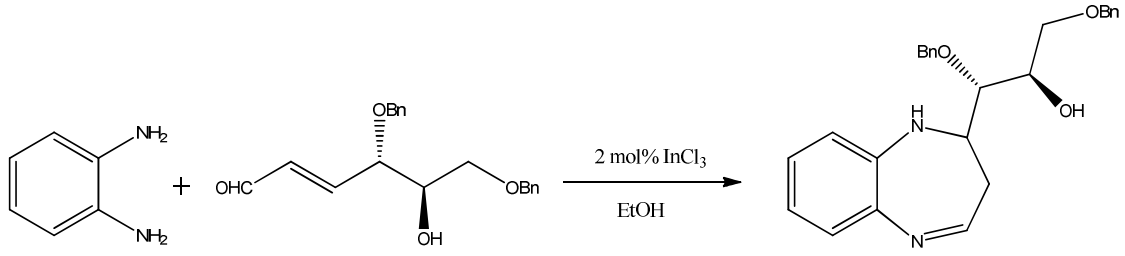
Tetranitrile-silver complex

Sreekumar K et al.[55] synthesized 1,5-benzodiazepines by using tetranitrile-silver complex as catalyst.



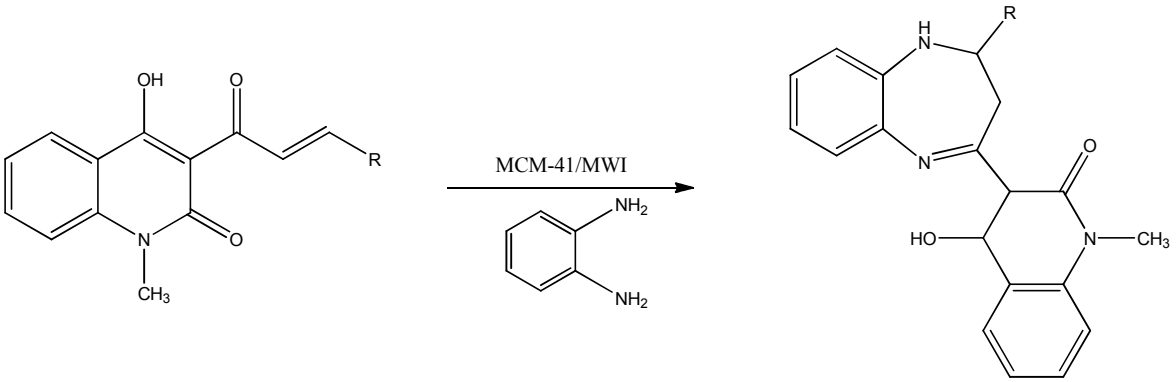
Indium chloride

Yadav JS et al.[56] used 2 mol% of $InCl_3$ (indium trichloride) under mild conditions to afford a new class of 1,5-benzodiazepines in good yields.

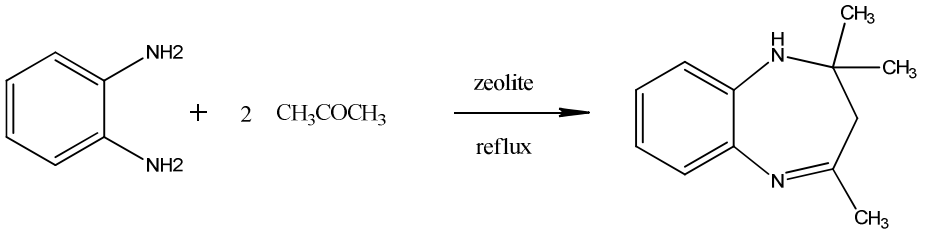


MCM-41 zeolite

Rao BV et al.[57] carried out an efficient synthesis of 1,5-benzodiazepines in an eco-friendly environment of microwave irradiation using MCM-41 zeolite as catalyst. The yields obtained were excellent (90-98%) and reaction time was short (5-10min).

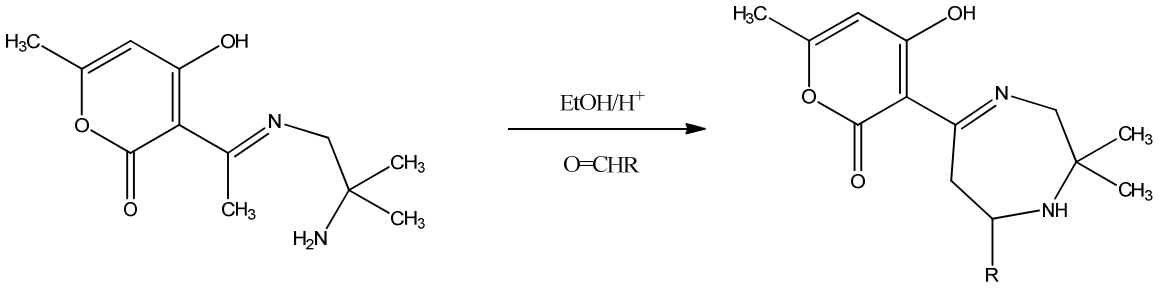


Heravi MM et al.[58] synthesized 1,5-benzodiazepines from the reaction of o-phenylenediamine and ketones in the presence of heterogeneous catalysis of synthetic and natural zeolites under mild conditions in very good yields and high selectivity.

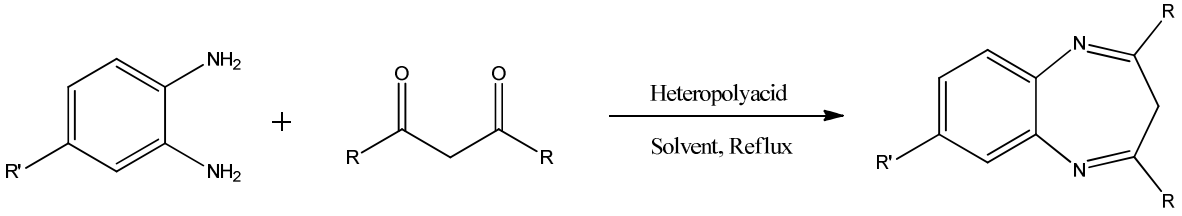


Heteropolyacids :

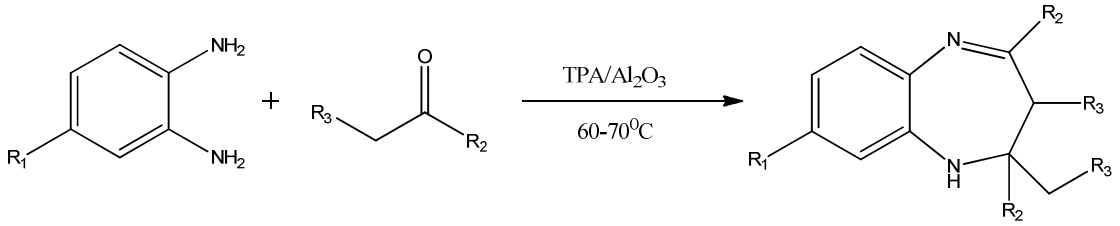
Nedjar-Kolli B et al.[59] synthesized 1,5-benzodiazepine derivatives via the reaction of ketimine intermediates with aldehydes in the presence of Keggin-type heteropolyacids (HPAs) was developed. High yields and short reaction times were obtained.



Heravi MM et al.[60] synthesized 3H-1,5-benzodiazepine derivatives from 1,3-diketones in the presence of various heteropolyacid (HPA) catalysts under mild conditions in very good yields and with high selectivity.

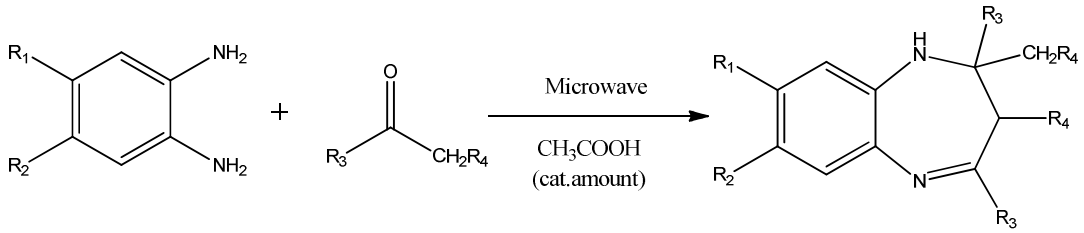


Alibeik MA et al.[61] synthesized 1,5-benzodiazepines using alumina supported 12-tungsto phosphoric acid in good to excellent yields (88-95%).



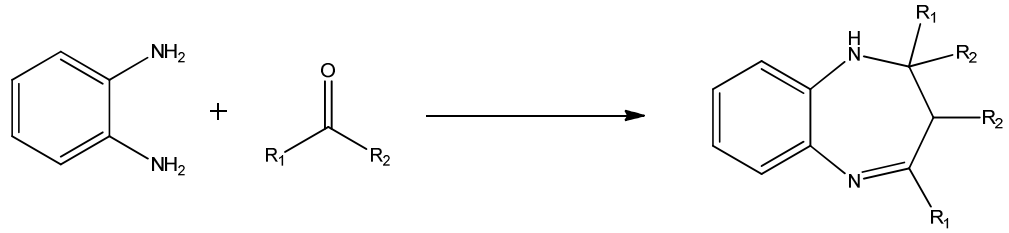
Acetic acid (Microwave irradiated)

Stephanatou J et al.[62] synthesized 2,3-dihydro-1H-1,5-benzodiazepines in solvent free conditions in the presence of a catalytic amount of acetic acid, under microwave irradiation. The yields obtained were excellent (90-99%).



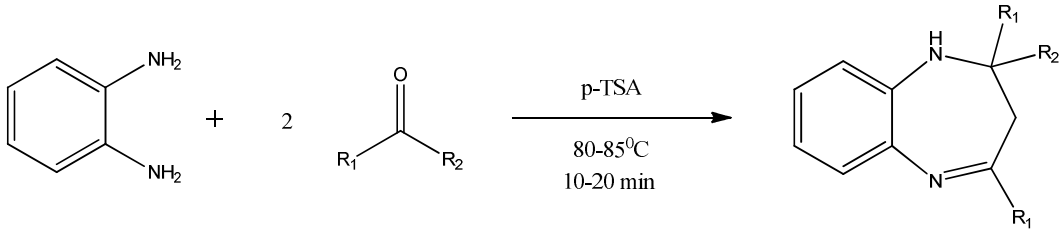
Ytterbium triflate Yb(OTf)$_3$

Curini M et al.[63] synthesized 2,3-dihydro-1H-1,5-benzodiazepines in very good yields (88-99%) in solvent-free conditions in the presence of $Yb(OTf)_3$ as catalyst.



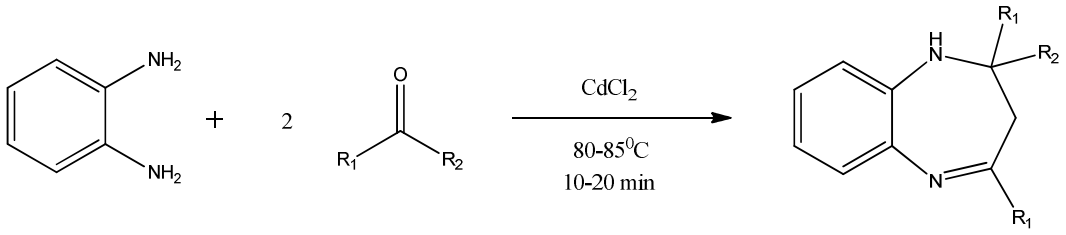
p-toluenesulfonic acid

Pasha MA and Jayashankara VP[64] synthesized 1,5-benzodiazepine derivatives in the presence of p-toluenesulfonic acid as catalyst. The yields are high and the reactions go to completion within 10-20 mins.



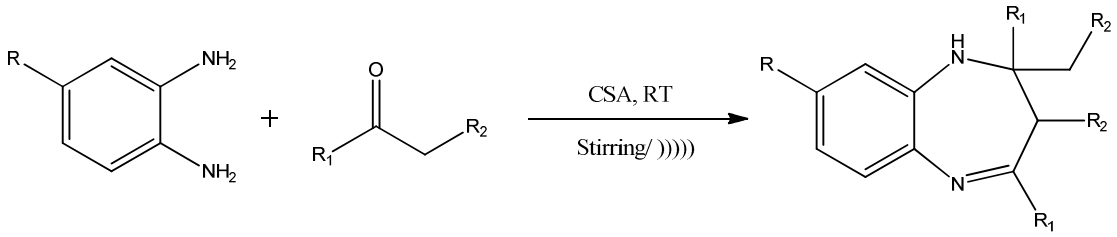
CdCl$_2$

Pasha MA and Jayashankara VP[65] synthesized 1,5-benzodiazepine derivatives in the presence of $CdCl_2$ as catalyst. The yields are high and the reactions go to completion within 10-20 mins.



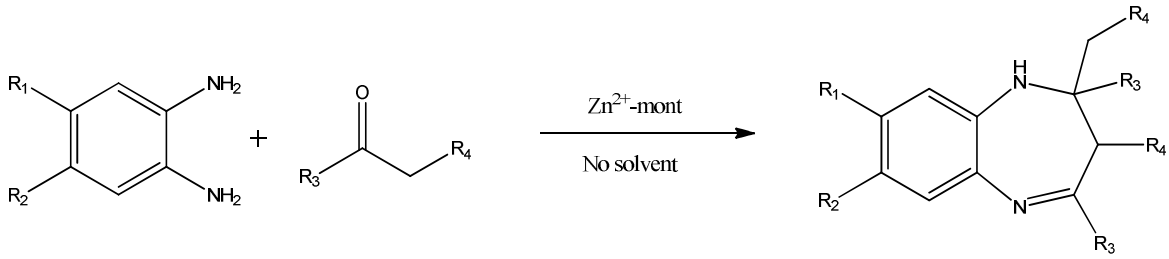
Camphor sulphonic acid (Ultrasound accelerated)

Shingare M et al.[66] demonstrated a successful implementation of ultrasound irradiations for the rapid synthesis of 1,5-benzodiazepine derivatives under solvent-free conditions. Use of a novel catalyst i.e. camphor sulphonic acid in combination with ultrasound technique was reported for the first time.



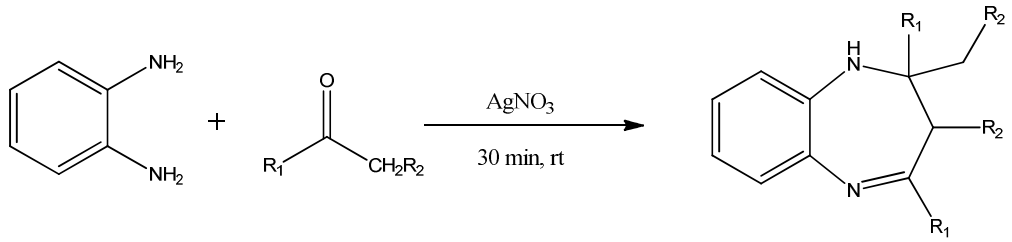
Zinc montmorillonite

Adapa S et al.[67] synthesized 2,3-dihydro-1H-1,5-benzodiazepines derivatives by using zinc montmorillonite as catalyst at room temperature.



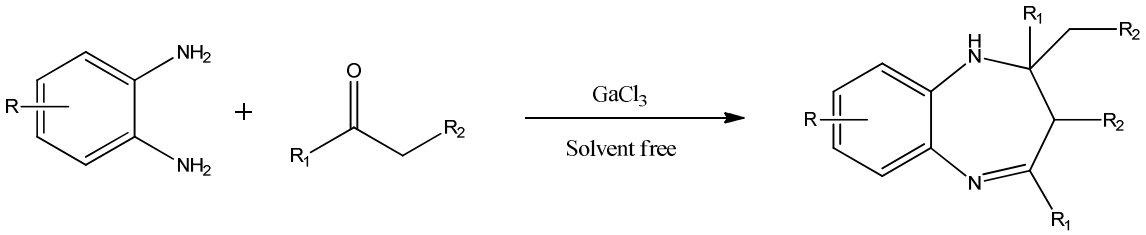
Silver nitrate

Chandra R et al.[68] synthesized 2,3-dihydro-1H-1,5-benzodiazepines in the presence of silver nitrate under solvent free conditions in good to excellent yields (84-99%).



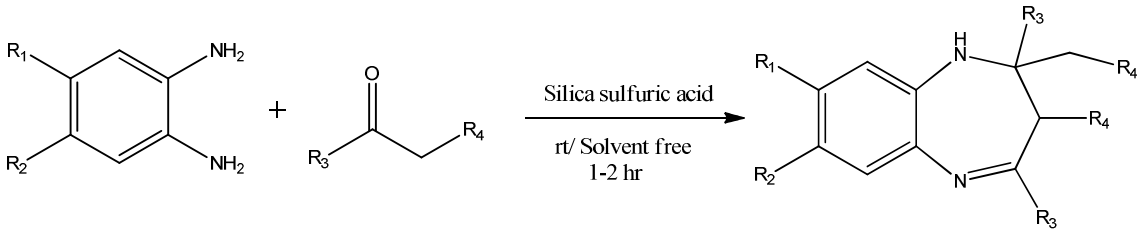
$GaCl_3$

Sandhu J and Kumar S[69] used $GaCl_3$ as catalyst for synthesizing 1,5-benzodiazepines under solvent free conditions in excellent yields (87-94%).



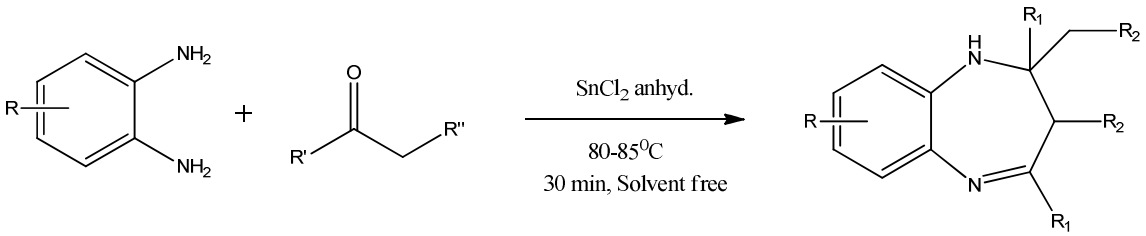
Silica sulfuric acid

Shaabani A and Ali M[70] synthesized 1,5-benzodiazepine derivatives by using silica sulphuric acid as catalyst under solvent free conditions. This proved to be a fast and efficient method where products were obtained in quantitative yields (90-98%).



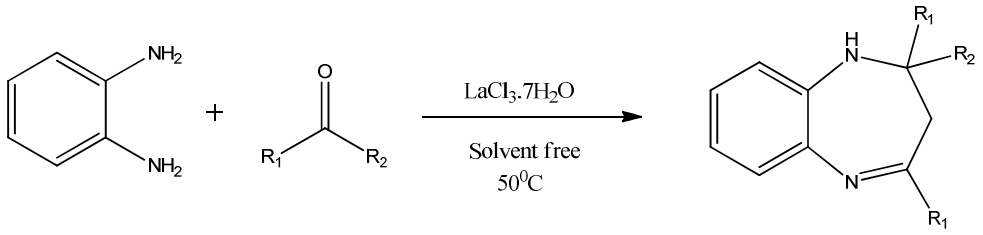
Stannous Chloride

Sharma S et al.[71] carried out one pot synthesis of 2,3-dihydro-1H-1,5-benzodiazepines under solvent free conditions using anhydrous stannous chloride as catalyst.



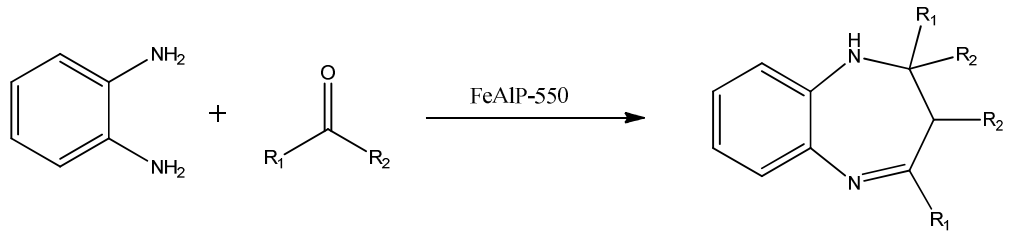
Lanthanum chloride ($LaCl_3.7H_2O$)

Pandit S et al.[72] synthesized 2,3-dihydro-1H-1,5-benzodiazepines under solvent free conditions in the presence of lanthanum chloride in catalytic amount. The products were obtained in high yields (80-91%).



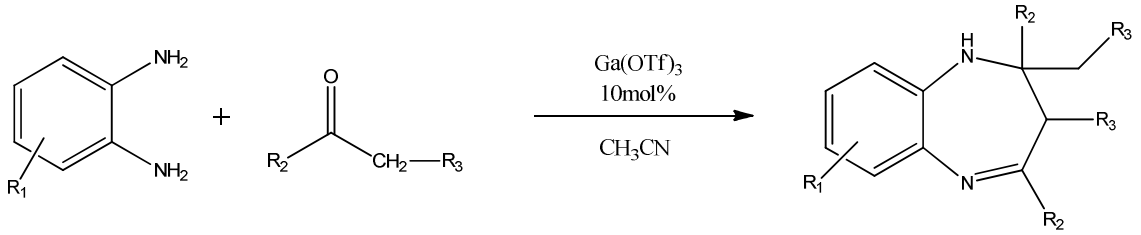
Amorphous mesoporous iron aluminphosphate

Nagaraju N et al.[73] demonstrated a simple and versatile method for the synthesis of 1,5-benzodiazepines in the presence of amorphous mesoporous iron aluminophosphate as catalyst. High yields with excellent selectivity of products were obtained.

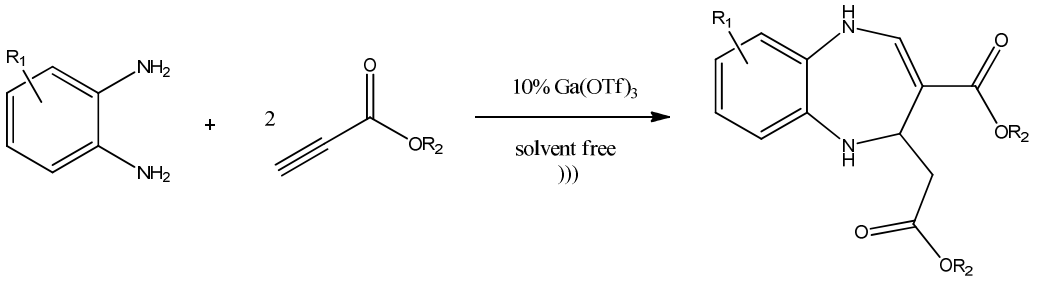


Gallium (III) triflate [Ga(OTf)$_3$]

Pan XQ et al.[74] synthesized 1,5-benzodiazepines in the presence of gallium (III) triflate i.e. Ga(OTf)$_3$ as catalyst. The products were obtained in good to excellent yields (70-92%).

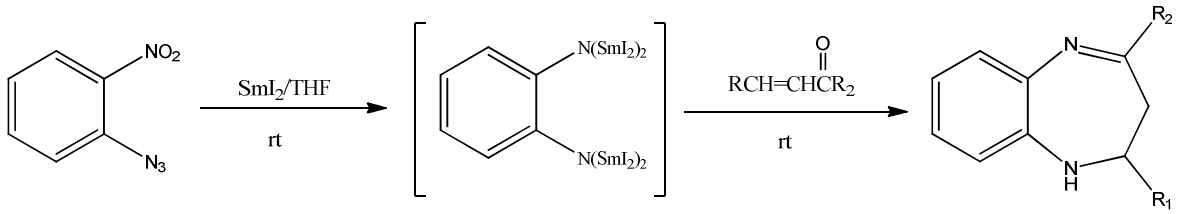


Zou JP et al.[75] carried out gallium(III) triflate-catalyzed [4+2+1] cycloaddition of o-phenylene diamines and 2 equiv of alkynoate under solvent-free and ultrasonic irradiation conditions, which afforded novel 3,4-disubstituted-1,5-benzodiazepines in 82–90% yields.



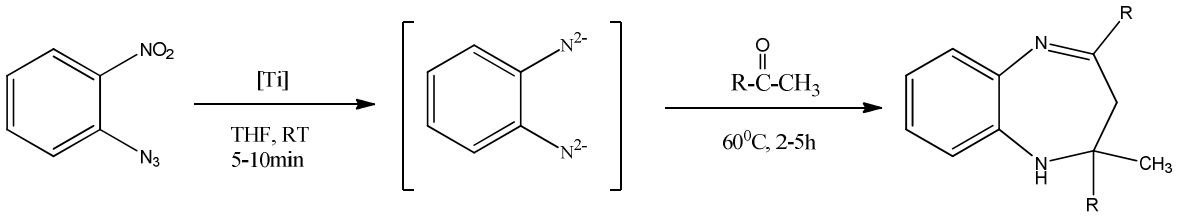
Samarium diiodide

Zhang Y et al.[76] demonstrated a new approach to 2,3-dihydro-1H-1,5-benzodiazepines promoted by samarium diiodide. The products were obtained in good yields (58-87%) under mild and neutral conditions.



TiCl$_4$/Sm system

Zhang Y et al.[77] synthesized 2,3-dihydro-1H-1,5-benzodiazepines in moderate to high yields(65-89%) under mild and neutral conditions in the presence of TiCl$_4$/Sm system as catalyst.



Pharmacological activities

A very diverse range of pharmacological activities have been shown by 1,5-benzodiazepine analogues. This proves the versatile nature of the benzodiazepine nucleus. A few of the biological activities demonstrated by 1,5-benzodiazepines in recent times are –

Anxiolytic[78] or anti-anxiety activity[79]
Antiviral activity[80, 81]
Antimicrobial activity[82,83]
Antifungal and anthelmintic[84]
Analgesic, anti-inflammatory and antipyretic activity[85]
Cholecystokinin-A receptor antagonistic activity[7]
Cholecystokinin-2 receptor antagonistic activity[6]

CONCLUSION

Based on the literature survey done, a lot of evidence has been provided that 1,5-benzodiazepines have a vast range of applications in the field of medicine and chemistry. They can be prepared via various routes of synthesis by using different starting materials. They can be synthesized by using a variety of different catalysts in solvent free conditions and also by employing numerous solvents. All the synthesized 1,5-benzodiazepine derivatives display a wide range of biological activities. Thus it has been proved that 1,5-benzodiazepine nucleus is an extremely versatile pharmacophore.

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benzodiazepine as Cholecystokinin-A receptor antagonists. Bioorg. Med. Chem,10: 3571-3581, (2002).
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