Heteropoly acid (DTP/SiO2) Catalyzed Environmentally Benign Synthesis of 4-substituted-1,5-benzodiazepine Derivatives

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Abstract:

A silica-supported dodecatungestophosphoric heteropoly acid (DTP/SiO_2) promoted cyclocondensation-cyclization pathway has been established using one pot reaction of benzene-1,2-diamine, 5,5-dimethylcyclohexane-1,3-dione and benzaldehyde, DTP/SiO_2 (12 mol%) and 10 ml DMF to give 1,5-benzodiazepine derivatives in good to promising yields. Application for this protocol easy workup, high yields, short reaction times, variability of functional groups, recyclability and solvent-free conditions.

Keywords: Heteropoly acid (DTP/SiO_2), Environmentally benign, Multicomponent reactions, 1,5-benzodiazepine

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Introduction

The multi-component reactions (MCRs), which have attracted significant attention during the past few years, do not occur through a single-step procedure, but rather via several sequential

steps involving cascades or domino reactions.[1a-f] MCRs are processes in which at least three different simple substrates react in one-pot to give the target materials.[2a,b] However, MCRs have contributed greatly in the convergent syntheses of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools in drug discovery.[3a,b] Simplicity, greater efficiency, atom economy and generation of molecular complexity with diversity in one-pot transformations are some advantages of these reactions.[4a,b]

Benzodiazepines (BZD)s and their polycyclic derivatives show a wide range of biological activities.[5] Benzodiazepines are the most frequently used psychotropic drugs because of their efficacy, rapid effect and low toxicity. Since the introduction of the first BZD (Chlordiazepoxide, in 1960, more than 50 BZD drugs have been synthesized for therapeutic applications.[6] Many bioactive compounds have been synthesized based on a 1,5- benzodiazepine scaffold such as clozapine, for the treatment of schizophrenia since 1982,[7] isoTIBO as HIV-1 non-nucleoside reverse transcriptase inhibitor,[8] imidazo (1,5)-benzodiaze- pine as an anti HIV agent,[9] and benzodiazepine **8** as a calcium channel blocking agent.

Nowadays, cancer has been one of the worldwide serious diseases that represent a real crisis for threatening human health and life.[10-12] Apart from the use of surgical treatment and irradiation, chemotherapy still remains the backbone of treatment against cancer.[13,14] However, one of the major hurdles in cancer chemotherapy is attributed to the prevalence of the drug and multidrug resistance.[15–17] Therefore, considerable efforts have been made on the design and the discovery of new anticancer agents focusing on the neotype chemical entity for the successful treatment of cancer,[18-24] anti HIV-1 activity,[25,26] hypnotic and anticonvulsant activities.[27] antimicrobial activity[28] neuroprotective agents,[29] Anti-obesity,[30] anti-schistosomal agents,[31] cholecystokinin-2 receptor antagonists,[32] anxiolytic activity,[33] antipsychotic Agents,[34] cytoprotective Activity,[35] antioxidant,[36] cholecystokinin-B receptor antagonists,[37] $GABA_A$ receptors,[38] antihypoxic and tranquilizing activity,[39] Hepatitis C virus (HCV) NS5B inhibitors,[40] antiinflammatory,[41a] antibacterial,[41b] antidepressant,[41c] hypnotic,[41d] anticoagulant,[41e] antiepileptic[42a,b] and analgesic agents[42c] shown in **Figure 1**.

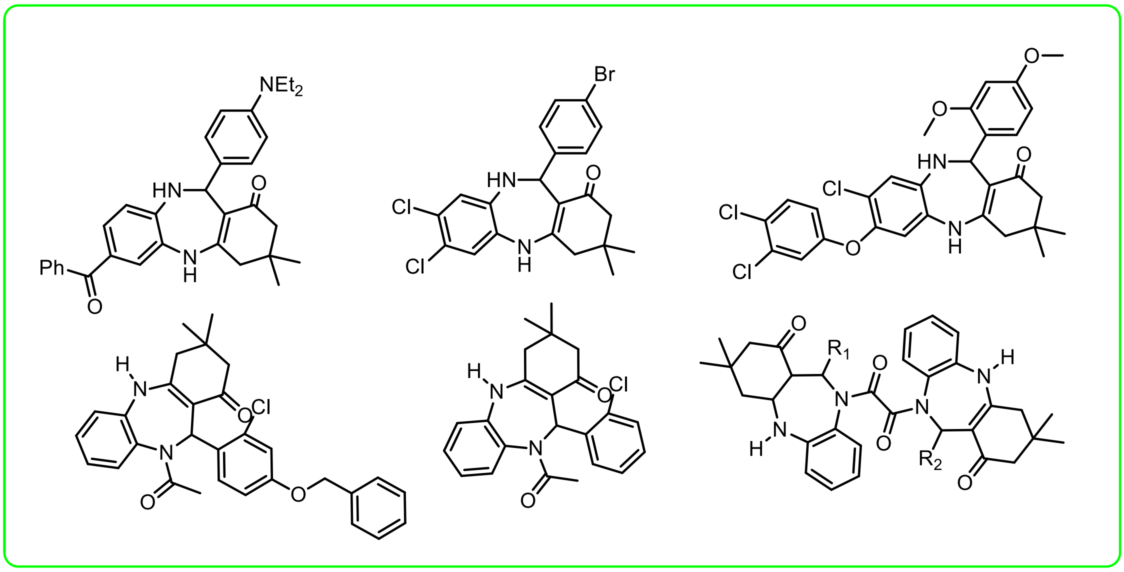


Figure 1. Structures of benzodiazepin with various biological activity

Some methods for the synthesis of 1,5-benzodiazepine derivatives have been reported in the literature via the condensation of one equivalent o-phenylenediamine with various aldehydes or ketones in the presence of a wide variety of catalysts, including SmI2 in the presence of molecular sieves at room temperature,[43] HBF_4-SiO_2 under solvent-free conditions,[44] $Yb(OTf)_3$,[45] SiO_2,[46] AcOH as catalyst under microwave irradiation,[47] SiO_2-H_2SO_4 catalyst under grinding microwave method,[48] C_6F_5COOH,[49] $Ga(OTf)_3$ in CH_3CN,[50] amorphous mesoporous iron alumino phosphate (FeAlP-550) as catalyst under solvent-free condition,[51] Fe_3O_4 nanoparticles,[52] $Hg(OTf)_2$,[53] and CF_3COOH in the presence of dehydroacetic acid (DHA).[54] Furthermore, the synthesis of 4-substituted-1,5-benzodiazepine derivatives have been carried out by three component condensation of o-phenylenediamine, dimedone and aldehydes by using AcOH in ethanol,[55] acetic acid,[33] oxalic acid in water,[56] AcOH in water under microwave condition,[57] acetic acid in toluene,[58] H_2SO_4,[59] HCl,[60] as Brønsted catalysts. Some of the other reported catalysts for this reaction are $Er(OTf)_3$ in CH_3CN,[61-62] and AcOH in the presence of 2,2-dihydroxy-1-phenylethanone under microwave irradiation.[63] Also, the hetero-Cope rearrangement protocol reported the synthesis of these compounds via condensation of 2-formyl benzoic acid with o-phenylenediamine and tetronic acid in water under microwave irradiation.[56] A unique gold (I)-catalyzed synthesis of 1,5-benzodiazepines directly from o-phenylenediamines and alkynes was achieved for the first time by Xu and co-workers,[64] and was developed by Luo et al.[65] Recently, the synthesis of benzodiazepines was reported by catalytic three-component coupling reaction of aromatic diamines, Meldrum's acid, and isocyanides.[66]

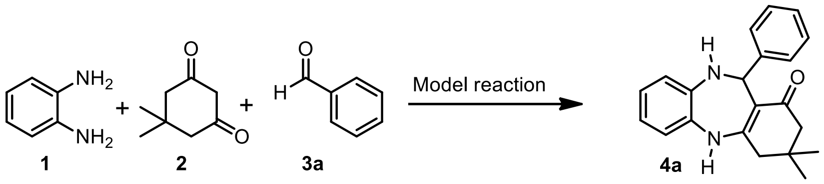
Heteropolyacids are excellent alternatives for conventional reagents and are usually used in various organic transformations. Solid acids as heterogeneous catalysts have been extensively used and accepted stratagem in organic synthesis. Literature survey shows that silica-supported heterogeneous catalyst DTP/SiO2 (dodecatungestophosphoric acid) is better than the conventional homogeneous acid catalysts due to its low cost, simple operation, low toxicity, and environmental compatibility.[67-69] In addition to this, the catalyst can be easily recovered from the reaction mixture only by filtration and reused, which leads to making the process affordable.

In conjunction with ongoing to preparation of heterocyclic compounds, we report an efficient and novel method for the synthesis of 4-substituted-1,5-benzodiazepine in high yields with high purity, using DTP/SiO2 recyclable heterogeneous catalyst under thermal conditions. The development of MCRs and improvement of known multicomponent reactions is a route of considerable interest. This green procedure has many obvious advantages compared to those reported in the previous literature,[1-4] including avoiding the usage of harmful catalysts, easy workup of the reaction, excellent yields and simplicity of the methodology.

Chemistry:

In this work, a simple energy, eco-friendly and convenient method for the synthesis of 4-substituted-1,5-benzodiazepine using DTP/SiO2 heterogeneous catalyst was described. Initially, in order to optimize the reaction conditions, the reaction of dimedone, o-phenylenediamine and benzaldehyde was carried out in an equal ratio to afford the benzodiazepines (**Scheme 1**), under various reaction conditions for an appropriate time (**Table 1**).

Present Work



Scheme 1. Model reaction

Table 1. Optimization of reaction conditions of solvent and temperature for the synthesis of 3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-*1H*-dibenzo[b,e][1,4]diazepin-1-one **4a**[a]

Entries	Solvent	DTP/SiO_2 mol %	Time (min)	Temp (°C)	Yield[b] (%)
1	EtOH	40 wt% (12 mol %)	30	Reflux	62
2	MeOH	40 wt% (12 mol %)	30	Reflux	68
3	*tert*-BuOH	40 wt% (12 mol %)	30	Reflux	67
4	H_2O	40 wt% (12 mol %)	30	Reflux	42
5	CH_3CN	40 wt% (12 mol %)	30	Reflux	46
6	THF	40 wt% (12 mol %)	30	Reflux	45
7	$PhCH_3$	40 wt% (12 mol %)	30	Reflux	54
8	IPA	40 wt% (12 mol %)	30	Reflux	62
9	DMF	**40 wt% (12 mol %)**	30	**90**	**93**
10	DMF	40 wt% (12 mol %)	30	60	68
11	DMF	40 wt% (12 mol %)	30	70	75
12	DMF	40 wt% (12 mol %)	30	80	91
13	DMF	40 wt% (12 mol %)	30	100	90
14	DMF	20 wt% (12 mol %)	30	90	60
15	DMF	60 wt% (12 mol %)	30	90	92

[a]Reaction conditions: benzene-1,2-diamine **1** (1 mmol), 5,5-dimethylcyclohexane-1,3-dione **2**, (1 mmol) and benzaldehyde **3a** (1 mmol), DTP/SiO_2 (12 mol%) and 10 ml DMF. [b]isolated yield

Then, we investigated the influence of various organic solvents at different reaction temperatures on the model reaction with 12 mol% of DTP/SiO_2. Among the various solvents, such as toluene, DMF, methanol, ethanol, THF, CH_2Cl_2, and acetonitrile, the rate of the reaction was very slow and resulted in lower product yields (**Table 1**, entries 1-7). Conducting the same reaction in acetonitrile improved both the reaction rate as well as the product yield (**Table 1**, entry 6). We also investigated different temperatures for the model reaction (**Table 1**, entries 8-11). It was observed that the reaction occurred rapidly on increasing the temperature from 60 °C to 100 °C, and the yield of preferred product increased significantly. We were satisfied to find that the reaction proceeded smoothly and almost a complete conversion of reactants was observed at 90 °C to afford the desired product **4a** in 93% yield within 30 min under DMF act as solvent. (**Table 1**, entry 9). Further increasing the temperature did not affect the product yield. However, better product yield was observed in DMF used as a solvent (**Table 1**, entry 9) and could be explained by the fact that a uniform distribution of the eutectic mixture of reactants was in closer proximity to react. From all these observations, we concluded that 12 mol% of DTP/SiO_2, 90 °C and DMF are the optimized reaction conditions

Moreover, we found that the yields were obviously affected by the amount of DTP/SiO_2 loaded. When 4 mol%, 8 mol%, 12 mol% and 16 mol% of DTP/SiO_2 were used, the yields were 60%, 93% and 92%, respectively (**Table 2**, entries 1-4). Therefore, 12 mol% of DTP/SiO_2 was found to be sufficient and no more significant improvement in the reaction rate and product yield was observed on increasing the amount of the catalyst from 4 to 16 mol% (**Table 2**, entry 4).

Table 2. The effect of catalyst loading on model reaction **4a**[a]

Entries	Catalyst Mol %	Solvent	Time (min)	Temp (°C)	Yield[b] (%)
1	4	DMF	30	90	60
2	8	DMF	30	90	75
3	12	DMF	30	90	93
4	16	DMF	30	90	92

[a]Reaction conditions: benzene-1,2-diamine **1** (1 mmol), 5,5-dimethylcyclohexane-1,3-dione **2**, (1 mmol) and benzaldehyde **3a** (1 mmol), DTP/SiO_2 (12 mol%), [b]isolated yield

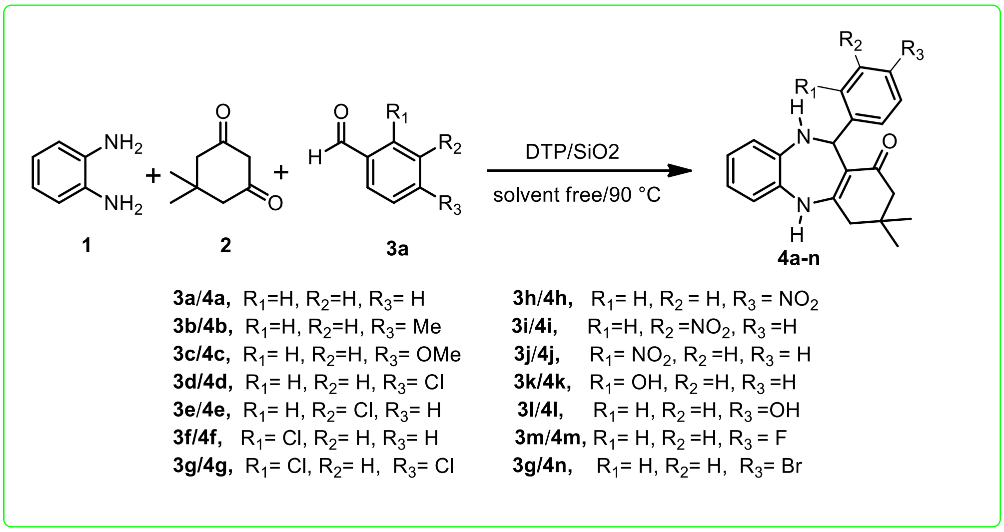
To investigate the catalytic activity and the possibility of the catalyst recyclability and reusability of the catalyst for the model reaction of benzene-1,2-diamine **1** (1 mmol), 5,5-dimethylcyclohexane-1,3-dione **2**, (1 mmol) and benzaldehyde **3a** (1 mmol) in DMF solvent at 90 C for 30 min and results were depicted in table 3.

Table 3. Reusability of DTP/SiO_2 in the synthesis of **4a**[a]

Entry	Reaction cycle	Isolated yield (%)[b]
1	1st (fresh run)	93
2	2nd cycle	91
3	3rd cycle	88
4	4rd cycle	88

[a]Reaction conditions: benzene-1,2-diamine **1** (1 mmol), 5,5-dimethylcyclohexane-1,3-dione **2**, (1 mmol) and benzaldehyde **3a**, (1 mmol), DTP/SiO_2 (12 mol%), [b]isolated yield.

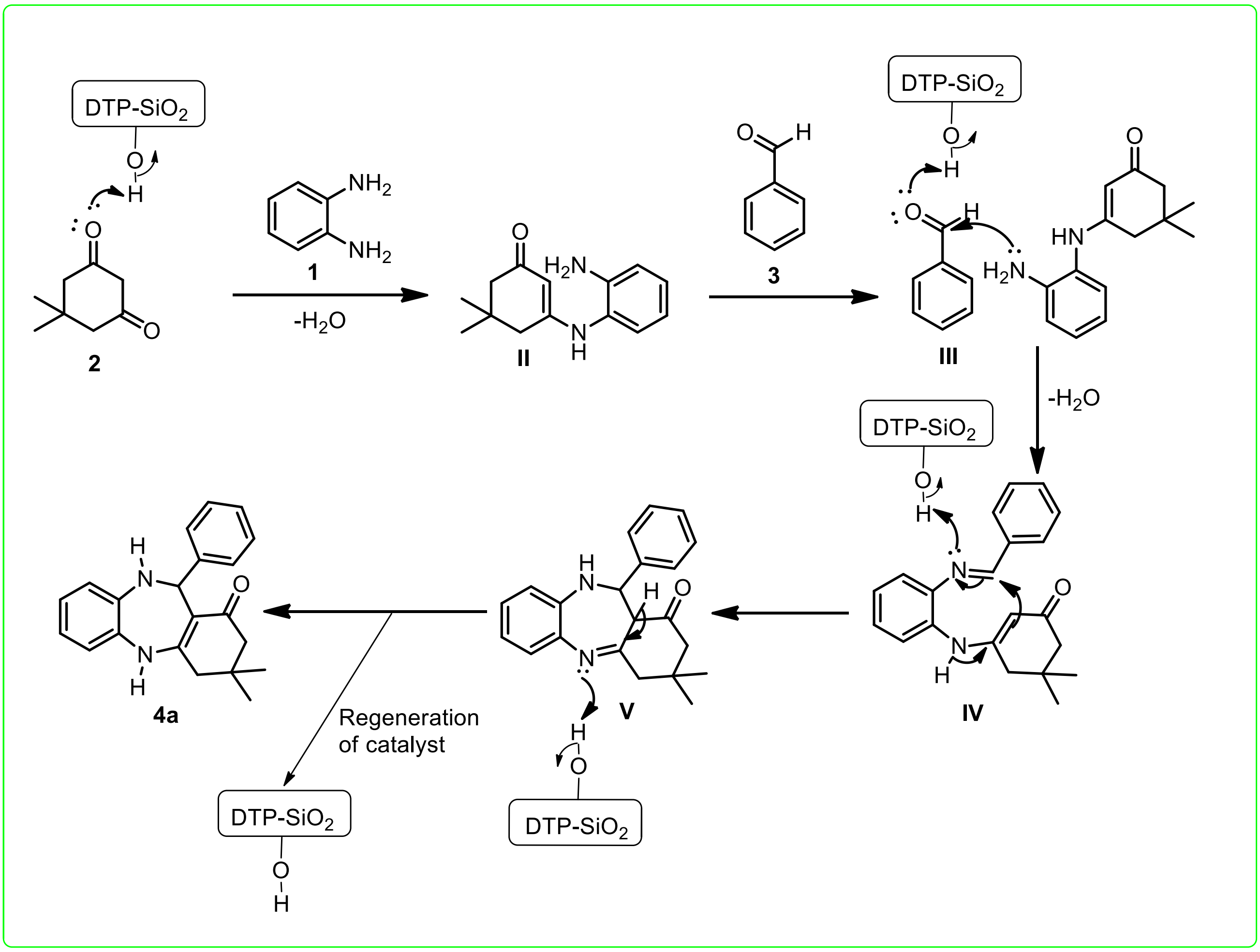
In general, in the development of this protocol, the reaction of o-phenylenediamine, dimedone with various aryl aldehydes was carried out according to the general experimental procedure. In all of the cases, the corresponding benzodiazepines were obtained in high to excellent yields and short reaction times. The obtained similar products are summarized in **Scheme 1**.



Scheme 1. Synthetic pathway for the synthesis of 4-substituted-1,5-benzodiazepine derivative

Furthermore, a wide variety of aldehydes (aromatic) with various substituents were also examined to establish the catalytic importance of DTP/SiO_2 for this reaction. A wide range of ortho, meta and para substituted aromatic aldehydes undergo this one-pot multicomponent reaction with dimedone and o-phenylenediamine toward benzodiazepines in excellent yields. In all of the entries, the almost same performance of catalyst was observed for this cyclo-condensation toward the synthesis of the desired products (**Scheme 1** and **Figure 2**). The reaction profile was very clean and no side reaction products were formed.

The structure of the obtained products was confirmed using ^{1}H NMR, ^{13}C NMR and HRMS spectroscopic data. In the ^{1}H NMR spectrum of compound **4a** exhibited two singlet bands for two methyl groups at δ = 1.08 ppm and δ = 1.03 ppm. Also, an quartet signal at δ = 2.11 ppm with J = 16 Hz for CH_2 protons, a signal at δ = 2.56 ppm for CH_2-C=O protons, a signal at δ = 5.71 ppm for NH proton, a signal at δ = 6.08 ppm for CH proton and a signal at δ = 8.69 ppm for -NH protons are presented in this spectrum. Similarly, the formation of the 4-substituted-1,5-benzodiazepine **4a** was also proven by the in the ^{13}C NMR spectra appearance of the peaks at δ 53.1, 52.6, 29.8 and 27.6 ppm shows that (-CH, CH_2 and CH_3 groups, respectively. Peak observed at δ 191.1 ppm due to the C=O group present in the target compound.



Scheme 2. Proposed mechanism for the formation of **4a**

The formation of 4-substituted-1,5-benzodiazepine from o-phenylenediamine, dimedone and aldehyde in the presence of DTP/SiO_2 as an efficient catalyst can be explained. A mechanism for the DTP/SiO_2 catalyzed one pot synthesis of 4-substituted-1,5-benzodiazepine is proposed. The desired product was formed in this reaction catalyzed by DTP/SiO_2 following various steps (**Scheme 2**). The role of DTP/SiO_2 occurs in steps **II** and **III** where they catalyze the Michael type coupling of dimedone with o-phenylenediamine and intermediate A with the aldehyde. Also, they catalyze the Knoevenagel type coupling in step **V** for seven membered ring cyclization, finally giving 4-substituted-1,5-benzodiazepine as the final product (**Scheme 2**).

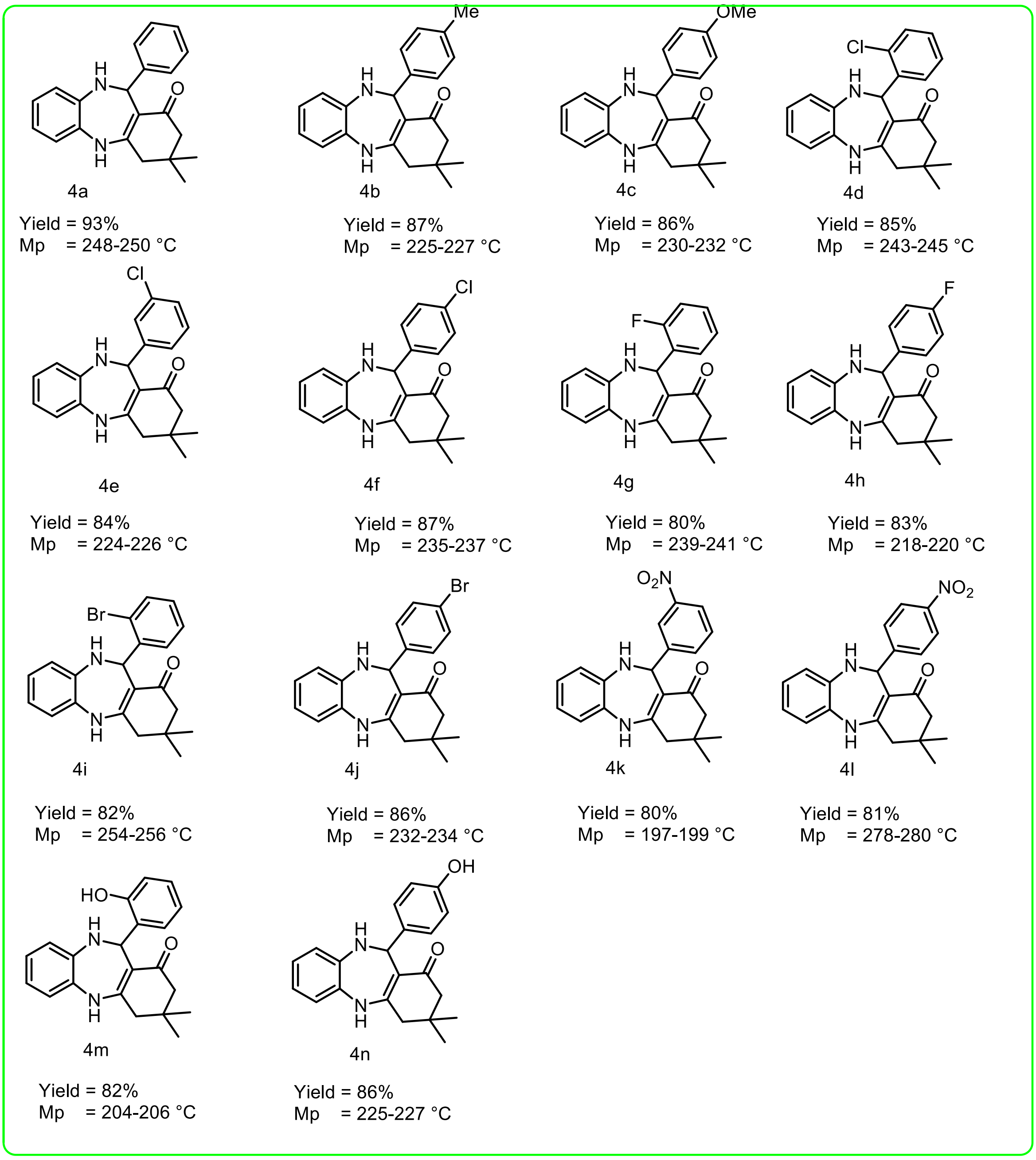


Figure 2. Structures, yields and melting point of 3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-*1H*-dibenzo[*b,e*][1,4]diazepin-1-one analogues **4a-n**

General procedure for the preparation of DTP/SiO_2

DTP impregnate SiO2 (20% DTP/SiO2) catalyst was prepared by an incipient wetness technique.[67] Firstly, 2 gm of dry dodecatungstophosphoric acid (DTP) was dissolved in 10 ml of methanol. The solution was added in a small portion of 1 mL each time to the silica with constant stirring with a glass rod properly. The solution was added at time intervals of 2 min. Initially, on the addition of the DTP solution, silica was in a powdery form but on complete addition, it formed a paste. The paste on further kneading for 20 min resulted in a free-flowing powder. The performed catalyst was dried at 120 C for removal of water and other volatiles and subsequently calcinated at 285 C for 3 h.

Conclusion

A highly efficient and environmentally benign protocol has been developed for the synthesis of 4-substituted-1,5-benzodiazepine using an recoverable and inexpensive DTP/SiO_2 at 90 °C for 30 min. This reaction protocol many more advantages, such as uniqueness, high atom efficiency, clean reaction profiles, mild reaction condition, ecofriendliness, simple workup and without using any hazardous solvents.

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Availability of Data and Materials

Experimental section and supplementary data (copies of ^{1}H and ^{13}C NMR spectra of represented compounds) associated with this article can be found through the "Supplementary Content" section of this article's webpage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent for publication

No consent for publication was required

Ethics Approval and Consent to Participate

Not applicable.

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