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Research Article

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Solvent-Free Syntheses of 1,5-Benzodiazepines Using HY Zeolite as a Green Solid Acid Catalyst

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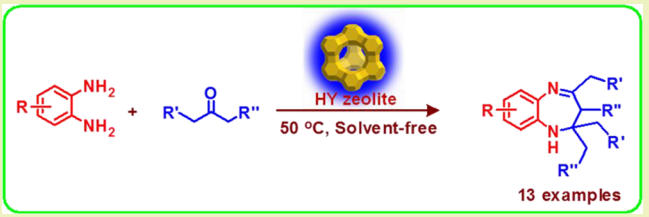
Supporting Information

ABSTRACT: 1,5-Benzodiazepines are synthesized from 1,2-diamines and ketones catalyzed by HY zeolite at 50 °C under solvent-free conditions. This process offers an easy and efficient synthesis of substituted 1,5-benzodiazepines in high yields. The advantages of this protocol are operational simplicity, nontoxicity, low cost, easy recovery, and an environmentally benign nature. The catalyst is recovered by filtration and reused six times without significant loss in its catalytic activity. A plausible mechanism is also proposed.



KEYWORDS: *1,5-Benzodiazepine, HY zeolite, Cyclization, 1,2-Diamine, Ketone, Solvent-free synthesis*

INTRODUCTION

1,5-Benzodiazepines are privileged heterocyclic ring systems because of their broad and important pharmacological properties.[1,2] These derivatives also find commercial applications as dyes for acrylic fibers in photography[3] and hypnotic agents,[4] as well as anti-inflammatory drugs.[5] In the past decade, the biological interest of 1,5-benzodiazepines have been extended to curing several diseases such as cancer, viral infections, and cardiovascular disorders.[6,7] Depending on the substitution pattern and nature of substituents, benzodiazepines can have a wide range of half-lives. Moreover, 1,5-benzodiazepines are key synthons for the synthesis of various fused ring systems such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[8−11] Over the past several years, considerable studies have been reported for the synthesis of 1,5-benzodiazepines utilizing ytterbium triflate,[12] gallium(III)-triflate,[13] erbium(III)triflate,[14] scandium(III)triflate,[15] ytterbium perfluorooctanesulfonate,[16] BF_3-etherate,[17] *p*-toulenesulfonic acid,[18] $NaBH_4$,[19] $MgO/POCl_3$,[20] polyphosphoric acid,[21] $CeCl_3$-NaI/SiO_2,[22] Al_2O_3/P_2O_5,[23] sulfated zirconia,[24] 1,3-*n*-dibutylimidazolium bromide,[25] $SbCl_3$-Al_2O_3,[26] iodine,[27] magnesium perchlorate,[28] sodium dodecyl sulfate,[29] $Ag_3PW_{12}O_{40}$,[30] zinc chloride,[31] dodecyl sulfonic acid,[32] piperidine acetic acid,[33] $La(NO_3)_3$,[34] SmI_2,[35] sulfamic acid,[36] organic acid,[37] $HClO_4$-silica,[38] $YbCl_3$,[39] ceric ammonium nitrate,[40] *N*-bromosuccinimide,[41] acetic acid/MW,[42] (NH_4)-$H_2PW_{12}O_{40}$,[43] $SnCl_2$,[44] K10-montmorillonite,[45] Zn-montmorillonite heterogeneous catalysts[46] borax/phosphorus oxychloride,[47] amberlyst-15,[48] $InBr_3$,[49] $InCl_3$,[50] $NbCl_5$,[51] and $RuCl_3 \cdot xH_2O$[52] as catalysts. In addition, a solvent-free procedure has been reported for the synthesis of 1,5-benzodiazepines using iodine,[53] silver nitrate,[54] and HBF_4-SiO_2[55] as catalysts at room temperature. However, in most homogeneous catalytic systems, the main problem is to remove the catalyst after the reaction, and therefore, reusability becomes impossible. Another concern with a homogeneous system is the presence of transition metal ions in the final heterocyclic product, and its removal requires tedious workup procedures. Consequently, in recent years, a considerable amount of research has been focused on the development of green chemical processes for organic transformations, particularly synthesis of heterocyclic compounds as viable alternatives to the already existing protocols.

In continuation of our work[56−59] on the applications of heterogeneous catalysts on organic transformations and also with a view to develop a green process for the synthesis of 1,5-benzodiazepines and to overcome the problems encountered in homogeneous systems, herein we report the synthesis of the title compound using HY zeolite as catalyst under solvent-free conditions. The main advantages of this methodology are the absence of solvents to perform the reaction, an inexpensive catalyst, and mild reaction conditions. Zeolites[60−67] are microporous crystalline aluminosilicates built from inifinitely extending a three-dimensional network of SiO_4 and AlO_4 tetrahedra that are linked together through oxygen bridges. By virtue of their structure, crystallinity, and variable stiochiometry, zeolite catalysts have well-defined pore size distributions, adjustable acidity, very high surface area, and good thermal stability.[68] Zeolites have been extensively used as powerful catalysts in organic transformations[69−75] due to their high stability and noncorrosive and nontoxic nature. In recent years, HY zeolite has been used as a catalyst in the synthesis of many heterocyclic compounds like imidazoles,[76] tetrahydrocarbazoles,[77] bis(indolyl)methanes,[66] 2-benzimidazoles,[78] poly-

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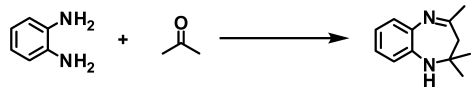
Table 1. Optimization of Reaction Conditions for the Synthesis of 1,5-Benzodiazepine[a]



entry	catalyst	amount of catalyst (mg)	solvent	time (h)	T (°C)	yield (%)[b]
1	–	–	neat	6	rt	–
2	–	–	neat	6	50	11
3	–	–	neat	6	75	12
4	HY	100	neat	6	rt	40
5	HY	100	neat	2, 4, 6	50	42, 93, 93
6	HY	100	neat	2, 4, 6	75	42, 93, 93
7	HY	50	neat	4	50	65
8	HY	150	neat	4	50	93
9	HY	200	neat	4	50	93
10	HY	100	chloroform[c]	6	50	61
11	HY	100	acetone[c]	6	50	55
12	HY	100	methanol[c]	6	50	60
13	HY	100	THF[c]	6	50	65
14	HY	100	DMF[c]	6	50	59
15	NaY	100	neat	6	rt	5
16	NaY	100	neat	6	50	30
17	NaY	100	neat	6	75	31
18	AlY	100	neat	6	50	53
19	FeY	100	neat	6	50	44
20	NiY	100	neat	6	50	49
21	CuY	100	neat	6	50	54
22	ZnY	100	neat	6	50	58
23	AgY	100	neat	6	50	56
24	BiY	100	neat	6	50	52
25	MgX	100	neat	6	50	50
26	Al-MCM-41	100	neat	6	50	69
27	Cu(BDC)	100	neat	6	50	48
28	Cu(BDC)	100	neat	6	75	49

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), acetone (2 mmol). [b]Isolated yield. [c]Solvent (5 mL).

hydroquinolines,[79] 1,4-dihydropyridines,[80] and substituted quinzolin-4(3*H*)ones.[81]

RESULTS AND DISCUSSION

The reaction conditions for the synthesis of 1,5-benzodiazepine from *o*-phenylenediamine and acetone as starting materials were optimized, and the observed results are given in Table 1. Blank experiments in the absence of catalyst at room temperature, 50°C, and 75 °C showed very minor amounts of product in 6 h (Table 1, entries 1−3). On the other hand, HY zeolite gave moderate yields of the desired product in chloroform, acetone, methanol, tetrahydrofuran, and N,N-dimethylformamide as solvent at 50 °C in 6 h (Table 1, entries 10−14). With a way to improve the yield of the product, the reaction was performed using HY zeolite in the absence of solvent. Surprisingly, the activity of HY zeolite gradually increased from room temperature to 50 °C, and the maximum yield (93%) was observed at 50 °C in 4 h under neat conditions. The effect of the amount of catalyst for the above reaction was also studied (Table 1, entries 5−9). These experiments showed that while an increase in yield was observed from 50 to 100 mg, it remained the same at 100, 150, and 200 mg (Figure 1). Further, increasing the reaction time to 6 h and temperature to 75 °C (from 50 °C) did not increase the yield, indicating that the optimal catalyst amount, reaction time, and temperature for the synthesis of 1,5-benzodiazepine are 100 mg, 4 h, and 50 °C. A thorough kinetic study for the

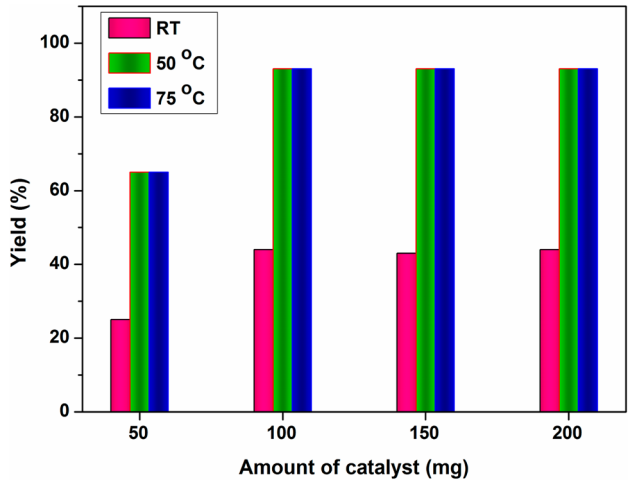


Figure 1. Reaction conditions: *o*-phenylenediamine (1 mmol), acetone (2 mmol), and HY zeolite, neat conditions.

noncatalyzed as well as catalyzed reactions at room temperature, 50 °C, and 75 °C was carried out, and the results are summarized in Figure 2. As expected, the noncatalyzed reactions showed lower yield compared to the HY zeolite-catalyzed reactions at different temperatures. However, HY zeolite-catalyzed reactions at 50 and 75 °C showed a similar kinetic profile, and the yield increased as a function of time and

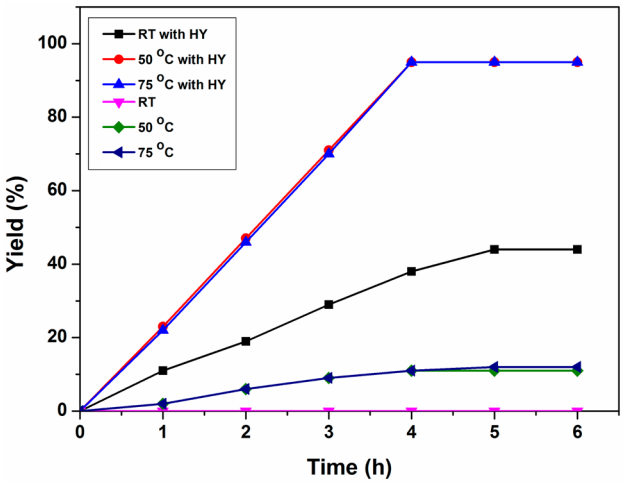


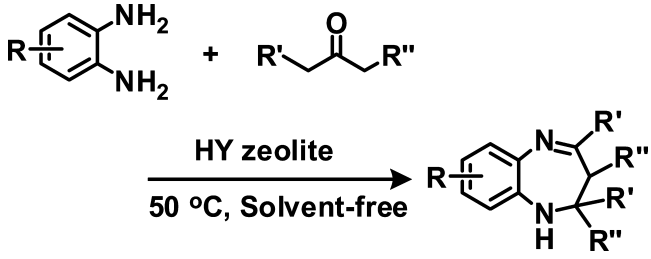
Figure 2. Reaction conditions: *o*-phenylenediamine (1 mmol), acetone (2 mmol), and HY zeolite (100 mg), neat conditions.

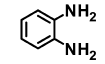
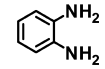
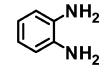
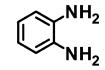
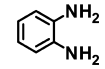
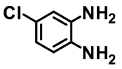
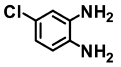
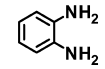
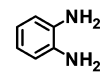
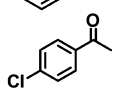
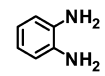
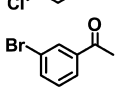
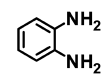
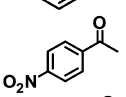
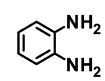
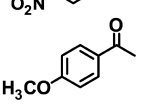
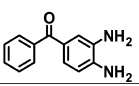
reached the maximum in 4 h and remained constant up to 6 h. These kinetic experiments clearly indicate that the temperature does not affect the yield of the product after 4 h.

In order to verify whether the reaction is catalyzed by Brönsted acidic sites or Lewis acidic sites of HY zeolite, the synthesis of 1,5-benzodiazepine was also carried out in the presence of various exchangeable metal cations like Na^{+}, Al^{3+}, Fe^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ag^{+}, Bi^{3+}, Mg^{2+}, and microporous Al-MCM-41 zeolites. With NaY zeolite, 5%, 30%, and 31% yields of the product were obtained at room temperature, 50 °C, and 75°C in 6 h (Table 1, entries 15−17). The results also clearly show that lower yields (Table 1, entries 16 and 18−26) were observed with metal-exchanged zeolites compared to HY zeolite (Table 1, entry 5). This indicates clearly the major role for Brönsted acidity of the HY zeolite in the title reaction. Metal organic frameworks (MOFs) are crystalline hybrid solids built from inorganic subunits (metal ions or clusters) and organic linkers bearing several complexing groups (carboxylates, phosphonates, imidazolates, etc.). Their easily tunable topology and composition, with sometimes high content of unsaturated metal sites, combined with their high porosity make these solids attractive candidates for heterogeneous catalysis, complementing other porous solids, such as zeolites and mesoporous metal oxides.[82,83] In this context, the catalytic behavior of HY zeolite is also compared with Cu(BDC) MOFs in the synthesis of 1,5-benzodiazepines, which resulted in 48% and 49% yield of the product at 50 and 75 °C, respectively, in 6 h.

These interesting preliminary results for the synthesis of 1,5-benzodiazepine prompted us to expand the scope of HY zeolite toward the synthesis of various 1,5-benzodiazepine derivatives under optimized conditions. To our surprise, we were able to synthesize a series of 1,5-benzodiazepines bearing different substitutions in very high yields. The reaction between substituted *o*-phenylenediamine and acetone resulted in the desired product in 81% yield after 4 h. In most cases, the reactions proceeded smoothly to give the respective products in satisfactory yields. An interesting correlation between the size of the reagents (ketone) and the reaction time is observed. With acetone, with smaller dialkyl ketone, good yield of the products were obtained in 4 h (Table 2, entries 1 and 6). Cyclic ketones like cyclohexanone also reacted to produce the corresponding fused ring 1,5-benzodiazepines (**3d**) in excellent

Table 2. Synthesis of 1,5-Benzodiazepine Derivatives Catalyzed by HY Zeolite[a]



entry	diamine	ketone	1,5-benzodiazepine	time (h)	yield[b] (%)
1			**3a**	4	93
2			**3b**	8	86
3			**3c**	8	89
4			**3d**	8	95
5			**3e**	8	88
6			**3f**	4	81
7			**3g**	8	75
8			**3h**	10	89
9			**3i**	10	85
10			**3j**	10	87
11			**3k**	10	83
12			**3l**	10	84
13			**3m**	8	80

[a]Reaction conditions: diamine (1 mmol), ketone (2 mmol), HY zeolite (100 mg), 50 °C, solvent-free conditions. [b]Isolated yield.

yield (Table 2, entry 4). As the size of the dialkyl ketone increases on butan-2-one and 4-methylpentan-2-one, corresponding products (**3c** and **3e**) were formed in good yields (Table 2, entries 3 and 5) but needed longer reaction time. It is interesting to note that the ring closure in these examples was selective from one side of the ketone giving a single product. Using acetophenone derivatives as one of the reactants, a longer reaction time was required. The effect of electron-withdrawing groups is not very significant in yielding the desired product (Table 2, entries 9−11, 13). These experiments clearly suggest that size of the reagent plays a significant role.

One of the main advantages of heterogeneous catalysts is the reusability after the completion of the reaction. In this context, the reusability of HY zeolite studied in the synthesis of 1,5-

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benzodiazepine from *o*-phenylenediamine and acetone under optimal conditions and the observed results are given in Table 3. After completion of the reaction, the catalyst was recovered

Table 3. Reusability of HY Zeolite in Synthesis of 1,5-Benzodiazepine[a]

run	1st	2nd	3rd	4th	5th	6th
yield[b] (%)	93	91	90	88	87	86

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), acetone (2 mmol), HY zeolite (100 mg), 50 °C, under solvent-free conditions for 4 h. [b]Isolated yield.

by filtration, washed with acetone, and dried at 80 °C for 3 h. The recovered catalyst was used for the next run under optimized reaction conditions. The results show that the catalyst is still efficient to promote this transformation even after the sixth run without much significant loss in activity. Further, we have carried out the kinetic studies of this catalytic system for each run under optimized conditions, and the observed results are given in Figure 3. These experiments

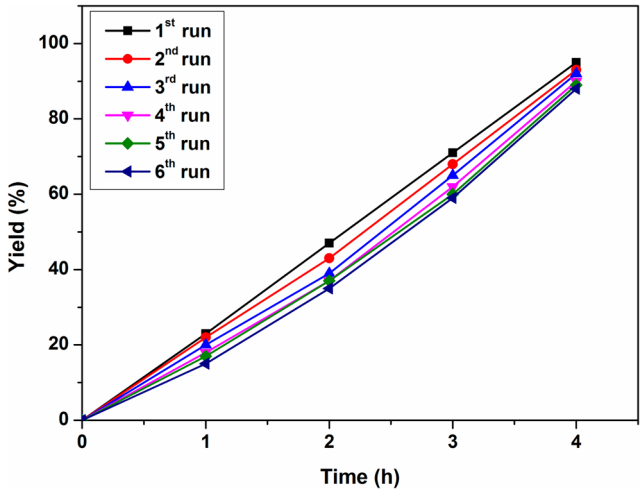

Figure 3. Reusability experiments using HY zeolite in synthesis of 1,5-benzodiazepine from *o*-phenylenediamine and acetone under neat reaction conditions as given in Table 3.

clearly demonstrate the robust nature of the catalyst and its stability by maintaining the activity and similar kinetic profile (Figure 3) even after six reuses, and these results will open a new avenue for further development on the catalytic activity of zeolites in heterocycle synthesis.

The reaction mechanism is proposed (Scheme 1) based on the reported literatures[17,19−21,25] for the condensation reaction involving polarization of ketone by HY zeolite *via* its Brönsted acidic sites, followed by nucleophilic attack of the aromatic group of *o*-phenylenediamine to yield mono-imine I. A similar sequence of events generates diamine II. Protonation of an imino group (N=C bond) by HY zeolite gives carbocation intermediate III, which being less stable undergoes a intramolecular hydrogen transfer from the high-leaving methyl group, with a resonance-stabilized more stable carbonium ion IV. Subsequent proton removal and intramolecular cyclization promoted by HY zeolite gives benzodiazepine.

Data on the reaction conditions, as well as the activity and efficiency of the different catalysts reported in the literature for the synthesis of substituted 1,5-benzodiazepine, are given in Table 4. These reported catalytic systems have their own advantages and disadvantages. In the case of amberlyst-15, which has poor thermal stability, it is not easy to recover because of its swelling in organic solvents, use of additives that are also needed for significant product selctivity, and a larger amount of catalyst that is required compared to our catalytic system. In the case of borax, it is hygroscopic in nature, and phosphorus oxychloride is corrosive and a hazardous compound. The other catalytic systems involve transition metal-mediated catalytic processes, and the catalysts are easy to recover by simple filtration. Taking all these into account, the use of HY zeolite as catalyst not only generates less waste but also has several advantages, which include insolubility in water/organic solvent, good catalytic activity, and high thermal stability. It is also nontoxic, environmentally benign, milder, inexpensive, and exhibits a wider substrate scope with higher selectivity and improved product yields. HY zeolite catalyst can also be easily recovered by simple filtration and can be reused many times without significant change of its activity. The catalyst is commercially available and easy to handle. A comparison of these results indicates that our catalytic system (Table 4, entry 10) exhibits better activity compared to conventional catalysts that require higher reaction time (entries 5 and 7), higher temperature (entries 2 and 6), and poor reusability of the catalyst (entries 1, 3, 4, 6, 7, and 9).

CONCLUSIONS

In conclusion, we have developed a simple and efficient method for the synthesis of 1,5-benzodiazepine derivatives from various substituted *o*-phenylenediamines and aliphatic/aromatic/cyclic ketones under mild and solvent-free conditions. The reaction was stopped when the catalyst was removed from the reaction mixture suggesting an active role of the catalyst in promoting the reaction and its true heterogeneity. High product yields were obtained, and the catalyst was recovered and reused several times. The salient features of this eco-friendly and environmentally benign process include an easy workup procedure, low cost of catalyst, and achieving high yield of products.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13} C NMR spectra were recorded on 400 and 100 MHz Bruker spectrometers, respectively. Coupling constants were reported in hertz (Hz). Reactions were carried out in an oven-dried three-necked round-bottomed flask. Yields reported here correspond to isolated yield of compounds as determined by ^{1}H and ^{13} C NMR analyses.

General Method for the Preparation of Cation-Exchanged Zeolites. NH_4Y zeolite powder is purchased from Sigma-Aldrich and used as received. The physiochemical parameters of the NH_4Y zeolite are a Si/Al ratio of 2.9, unit cell size of 24.68 Å, and surface area of 925 m^2/g with supercages of a diameter of ≈1.38 nm. HY zeolite was obtained by the thermal deammonification of NH_4Y zeolite at 450 °C for 6 h.

NaY zeolite powder was purchased from Sigma-Aldrich and used as received without further treatment. The physicochemical parameters of the NaY zeolite are a Si/Al ratio of 2.43, unit cell size of 24.65 Å, and surface area of 900 m^2/g with supercages of a diameter of ≈1.3 nm. Cation-exchanged zeolites (Al^{3+}, Fe^{3+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ag^{+}, and Bi^{3+}) are prepared by the ion-exchange method.[84] The cations of interest are exchanged into the NaY zeolite powder (10 g) by stirring with the corresponding nitrate solution (100 mL, 10%) at 90 °C for about 12 h. The exchange is repeated at least four times. Each time, after the exchange, the zeolite powder is washed repeatedly with

Scheme 1. Proposed Mechanism of Formation 1,5-Benzodiazepine Catalyzed by HY Zeolite

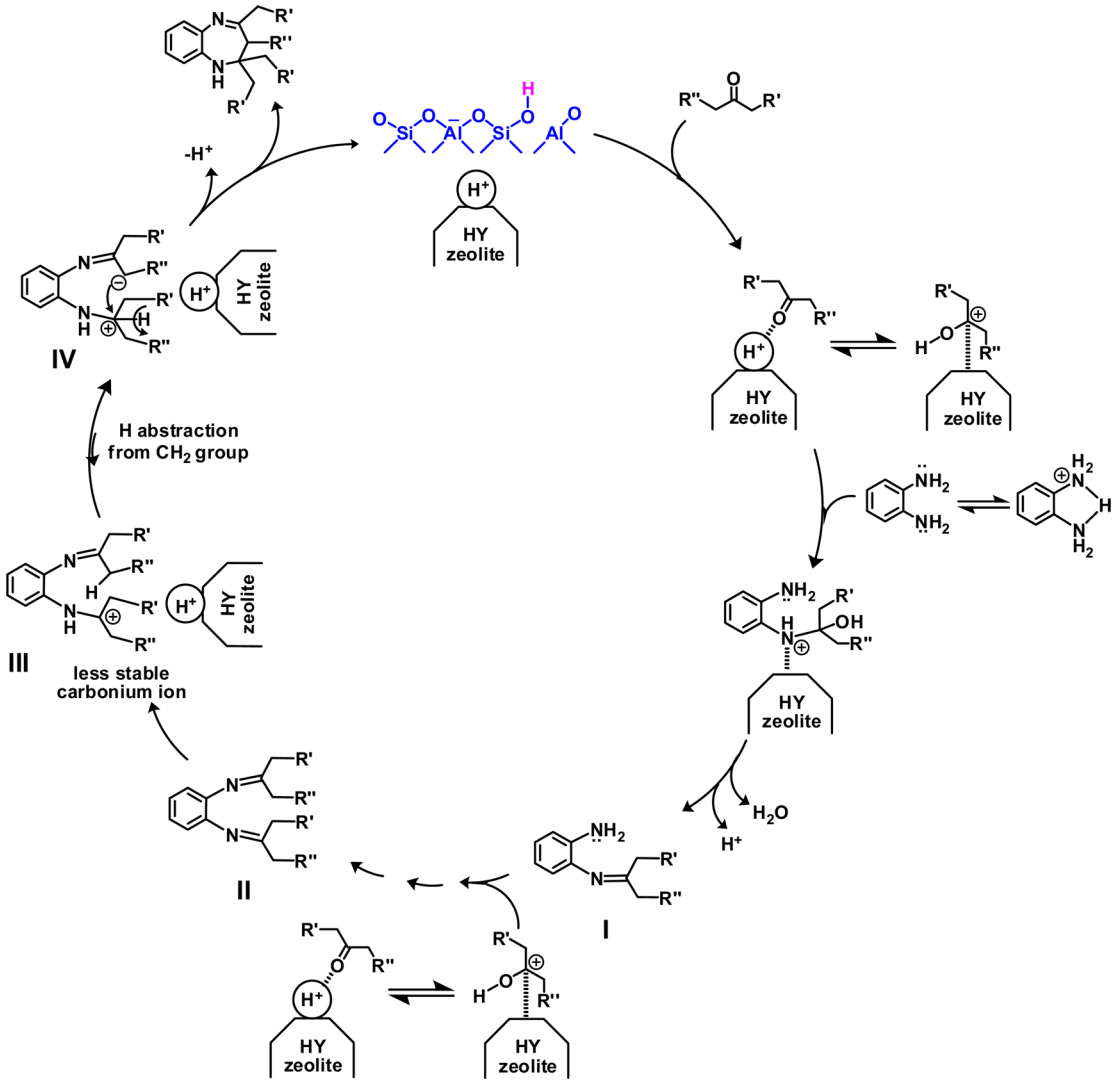

Table 4. Comparison of the Present Catalytic System with Earlier Reported Works for Synthesis of Substituted 1,5-Benzodiazepine from Substituted *o*-Phenylenediamine and Substituted Ketone

entry	catalyst (weight)	supporting reagent (weight)	solvent	T (°C)	time	yield (%)	reusability	ref
1	$Sc(OTf)_3$ (5 mol %)	NR	neat	rt	3 h	81–96	4(73)	15
2	$Yb(OPf)_3$ (0.04 mmol)	NR	perfluorodeclain	60	2 h	92–99	5(97)	16
3	sulfamic acid (0.050 g)	NR	neat	rt	3 h	22–83	2[a]	36
4	$HClO_4$-silica (50 mg)	NR	neat	rt	1–2 h	78–95	4(79)	38
5	$YbCl_3$ (0.05 mmol)	NR	neat	rt	12–36 h	49–98	4(95)	39
6	$(NH_4)H_2PW_{12}O_{40}$ (5 wt %)	NR	DCE	reflux	2–3 h	88–95	reusable[a]	43
7	K10-mont. (0.3 g)	NR	neat	rt	6–24 h	64–90	NR	45
8	borax/phosphorus oxychloride (0.1 g)	NR	neat	rt	0.5 h	87–95	4(89)	47
9	amberlyst-15 (0.75 g)	$[bmim]PF_6$ (2 mL)	neat	rt	3–6.5 h	80–95	4(81)	48
10	HY zeolite (100 mg)	NR	neat	50	**4–10 h**	75–**95**	**6(86)**	present system

[a]Data were not reported.

distilled water and then dried. All these cation-exchanged zeolites are activated at 450 °C for about 6 h prior to use.

Typical Procedure for Synthesis of 1,5-Benzodiazepine Derivatives Over HY Zeolite Catalyst. To a mixture of substituted *o*-phenylenediamine (1 mmol), ketone (2 mmol) and HY zeolite (100 mg) were added. This reaction mixture was mixed uniformly and heated at 50 °C until the completion of the reaction as monitored by TLC. Acetone (10 mL) was added to the reaction mixture after cooling the reaction mixture to room temperature, and the resultant heterogeneous solution was stirred for 2 h and filtered to remove the catalyst. The filtered catalyst was washed with ethyl acetate (2 mL × 10 mL), air-dried, activated, and reused for successive runs. The filtrate was dried over anhydrous sodium sulfate. The solvent was removed, and the residue was finally purified by column chromatography using hexane–ethyl acetate (20% ethyl acetate in hexane) as an eluent to afford pure 1,5-benzodiazepines. TLC is 7:3 (hexane:ethyl acetate).

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The products were confirmed by mass spectrometry, ^{1}H and ^{13}C NMR, and their melting points. HY zeolite was preactivated at 450 °C for 6 h in all the experiments.

■ ASSOCIATED CONTENT

Supporting Information

General information, characterization datas (^{1}H, ^{13}C NMR, and ESI-MS), and copy of ^{1}H and ^{13}C NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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