

Short communication

# Solid acid catalytic synthesis of 1,5-benzodiazepines: A highly improved protocol

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## Abstract

1,5-benzodiazepines were synthesized 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.

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## 1. Introduction

Benzodiazepines have interesting biological and pharmacological activities. This family of compounds are widely used as anti-anxiety, anti-convulsant, and hypnotic agents [1,2]. 1,5-Benzodiazepines are key intermediates for some fused heterocyclic rings such as triazol [3] and oxadiazole [4]. They also find commercial use as dyes for acrylic fiber in photography industry [5] and industrial scale production of anti-inflammatory agents [6].

Due to their wide range of pharmacological activity in synthetic and industrial applications, the synthesis of these compounds have recently received a great deal of attention for the discovery of improved protocols towards milder and high yielding approaches.

Generally, 1,5-benzodiazepines are synthesized by the condensation reaction of *o*-phenylenediamines with  $\alpha$ ,  $\beta$ -unsaturated compounds [7],  $\beta$ -haloketones [8], and ketones [9]. Among these methods, the acid catalyzed condensation of *o*-phenylenediamines with ketones is one of the simplest and most applicable approaches for the synthesis of 1,5-benzodiazepines.

A variety of catalysts such as  $\text{BF}_3 \cdot \text{OEt}_2$  [9],  $\text{NaBH}_4$  [10],  $\text{PPA-SiO}_2$  [11],  $\text{MgO-POCl}_3$  [12],  $\text{Yb}(\text{OTf})_3$  [13],  $\text{Al}_2\text{O}_3\text{-P}_2\text{O}_5$

[14],  $\text{HOAc-microwave}$  [15],  $\text{SO}_4^{2-}\text{-ZrO}_2$  [16],  $\text{I}_2$  [17],  $\text{InBr}_3$  [18],  $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$  [19],  $[\text{L}(\text{proline})]_2\text{Zn}$  [20], and ionic liquids [21] have been employed to affect this transformation. In recent years, organic syntheses using solid acid heterogeneous catalysis have been of great interest in view of a flowering environmental awareness [22]. In the last decade this approach has had abundant development mainly due to the use of zeolites. These catalysts can help to achieve new reactions to lower the vast production and to render more attractive the synthesis from both environmental and also the economic points of view [23,24]. Because of interesting application of 1,5-benzodiazepines and in continuation of our interest in heterocyclization reaction [25] and ongoing research in heterogeneous catalysis [26], in this communication we report our results for the synthesis of 1,5-benzodiazepines using synthetic and natural zeolites in a truly heterogeneous catalysis.

## 2. Experimental

### 2.1. Synthesis of 2,2,4-trimethyl-2,3-dihydro-1,5-benzodiazepines; typical procedure

To a stirred solution of excess acetone and 0.2 g of solid acid catalyst, which had been stirred for 1 h at room temperature, were added *o*-phenylenediamine (10 mmol) in acetone dropwise in period of 15 min. The mixture was refluxed for 3–7 h depending

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Table 1  
Comparison of specifications of some zeolites

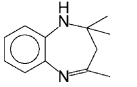
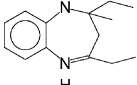
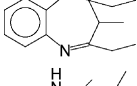
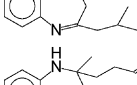
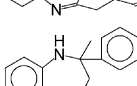
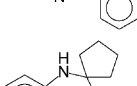
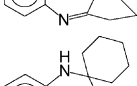
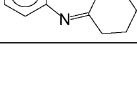
Entry	Catalyst	Si/Al	BET surface area (m <sup>2</sup> /g <sup>-1</sup> )	Ammonia uptake (mmol/g)
1	Heulandite	5	44	1.95
2	HY	2.5	490	0.53
3	HZSM-5	28	310	1.41

on the solid acid used (Table 2). The progress of the reaction was followed by TLC using 20% EtOAc in hexane as eluent. After the completion, the catalyst was separated by filtration and the excess acetone was removed under pressure. The reaction mixture was then diluted with water and extracted with chloroform. Subsequently, the solution was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The crude was subjected to further purification through a silicagel column using EtOAc: Hexane (2:8) as eluent to afford the pure product.

Similarly for other cyclic and acyclic ketones, we used this procedure using excess ketones, (*o*-phenylenediamine: ketone, 1:4) and in acetonitrile or dichloromethane solvents.

All compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples. The products were characterized by mp, IR, <sup>1</sup>HNMR, and MS.

Table 4  
Condensation of *o*-phenylenediamine with various ketones catalyzed by synthetic and natural zeolites

Entry	Ketone	Product	HY			Heulandite <sup>a</sup>			Ref
			Time (h)	T (°C)	Yield (%)	Time (h)	T (°C)	Yield (%)	
a	Acetone		3	50–55	82	5	50–55	81	[18]
b	3-Butanone		3	60–65	79	5	60–65	77	[18]
c	3-Pentanone		3	60–65	80	5	60–65	80	[13]
d	4-Methyl-2-pentanone		3	60–65	77	5	60–65	78	[19]
e	6-Methyl-5-hepten-2-one		3	60–65	78	5	60–65	76	[13]
f	Acetophenone		3	60–65	82	5	60–65	80	[20]
g	Cyclopentanone		4	70–75	65	6	70–75	62	[19]
h	Cyclohexanone		4	70–75	67	6	70–75	69	[19]

<sup>a</sup> Heulandite.

Table 2  
Experimental results using different zeolites

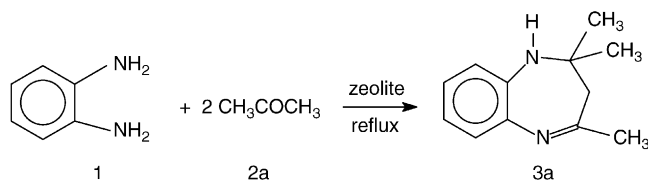
Entry	Catalyst	Wt.% of cat.	Time (h)	T (°C)	Yield % <sup>a</sup>
1	HEU	10	5	50–55	81
2	HY	10	3	50–55	82
3	HZSM-5	10	7	50–55	52

<sup>a</sup> Yields refer to isolated products.

Table 3  
The catalysts recycling studies

Run	HY		Heulandite	
	Time (h)	Yield (%)	Time (h)	Yield (%)
1	3	82	5	81
2	3	82	5	80
3	3	81	5	80
4	3	80	5	79
5	4	80	6	78
6	6	48	9	42

Data for **3a**: mp 135–137 °C; <sup>1</sup>HNMR(CDC<sub>13</sub>): 1.35 (s, 6H), 2.25 (s, 2H), 2.35 (s, 3H), 2.95 (brs, 1H, NH), 6.65–7.25 (m, 4H, arom); IR (KBr): 3340, 1650, 1600 Cm<sup>-1</sup>; MS: 188(M<sup>+</sup>), 173, 132, 104, 77.



Scheme 1. The specifications of some zeolites used in this reaction are given in Table 1.

### 3. Results and discussion

Recently, considerable attention has been devoted to heterogeneous organic transformation utilizing inorganic solid acids. Among the various solid acid catalysts investigated, zeolites have attracted much attention because of their suitable acidity, eco-friendliness availability, and low cost.

We have recently introduced a new Heulandite type of natural zeolite and used it to catalyze the Biginelli reaction [27]. During the course of our studies towards the development of this zeolite as an efficient heterogeneous catalyst, in this work, we have employed it and other synthetic zeolites such as HZSM-5 and HY for the one-pot condensation of *o*-phenylenediamine and acetone in the formation of 2, 2, 4-trimethyl-2, 3-dihydro-1H-1,5-benzodiazepine 3a (Scheme 1).

Zeolite Catalyst was added to excess acetone and the mixture stirred for 1 h at room temperature. At this point, the reaction mixture should contain self-condensation product. By addition of *o*-phenylenediamine (10 mmol), according to Suschitzky suggested mechanism [9], the self-condensation product was allowed to react to form the 2,2,4-trimethyl-2,3-dihydro-1,5-benzodiazepine.

As shown in Tables 1 and 2, HY and HEU are more efficient catalysts in this reaction in comparison with HZSM-5. This superiority may be due to the greater number of the Lewis acid sites (Al) and the weak acidic sites on the basis of TPD profiles [27]. Indeed containing weak Lewis acid sites, HY and Heulandite catalysts favor this progress of reaction and enhance catalytic performance due to the impossibility of denseness of the active sites. The catalysts can be recovered and used up to five times without any activity loss or product yields. The results are summarized for HY and Heulandite in Table 3.

This process was extended to other 1,5-benzodiazepine derivatives. The results disclosed in Table 4 show the scope and generality of the method. One of the salient features of this method is that both acyclic and cyclic ketones give high yields and purities. For instance, treatment of *o*-phenylenediamine with 2-butanone, acetophenone, and isobutyl methyl ketone under similar conditions gave the corresponding 1,5-benzodiazepines in 70–80% yields.

Cyclic ketones worked also well to afford fused ring 1,5-benzodiazepines in good yields. The reactions have also been carried out under both excess ketones and in acetonitrile or dichloromethane. No differences in yields or even reaction times were observed in either case.

### 4. Conclusion

In conclusion, we have developed a method using some commercially available, inexpensive, and reusable solid acid catalysts for the synthesis of 2,3-dihydro-1H-1,5-benzodiazepines from *o*-phenylenediamine and cyclic or acyclic ketones containing hydrogens at *o*-position. The reasonable reaction times, very good yields, simple workup procedure, and environmentally friendly conditions are main merits of this method.

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