



Research Article

## Synthesis of 2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine using Treated Natural Zeolite Catalyst

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### Abstract

The cyclocondensation of 1,2-phenylenediamine and acetone in the presence of treated natural zeolite catalyst (TNZ) under solvent-free condition has been done. The research consisted of three steps. The first step was treatment of natural zeolite by mixing this material in hydrochloric acid solution at 50 °C for 1 hour to be followed by soaking the zeolite in ammonium chloride solution for 5 days. The second step was solvent-free condensation of 1,2-phenylenediamine and acetone using TNZ at 50 °C for 2 hours with weight ratio variation of catalyst, i.e. 15, 30, 45, and 60% (wt/wt). The third step was to study catalyst reusability for the condensation reaction. Based on TLC, FTIR, and <sup>1</sup>H NMR analyses, the condensation afforded 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine as the product in 73% yield with the optimum of catalyst loading at 30% (wt/wt). The reusability test showed that the catalyst can be reused for the cyclocondensation for four times. Copyright © 2019 BCREC Group. All rights reserved

**Keywords:** 1,5-Benzodiazepine; Catalyst Reusability; Heterogenous Catalyst; Natural Zeolite; Solvent-Free

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### 1. Introduction

This 1,5-Benzodiazepine, an important class of biologically active N-containing heterocyclic compound, shows various pharmacological properties for example antidepressive, antiallergic, antiinflammatory, antipyretic, analgesic, anti-convulsant, hypnotic, antianxiety, anti-ulcerative, antihistaminic [1]. Along with the appliances in medical treatment such as cardiovascular diseases, schizophrenia, and cancer [2,3], the application of 1,5 benzodiazepine de-

rivatives has further been used in the field of photography as dyeing acrylic fibre [4], key synthetic intermediate, known as a synthon, leading to a variety of fused ring products [5-7], and antimicrobial agents [8]. Extensive research on benzodiazepine synthesis has been reported due to its enormous pharmacological and commercial importance.

Generally, 1,5-benzodiazepines can be synthesized by cyclocondensation of o-phenylenediamine and ketones using homogenous catalyst, i.e. CH<sub>3</sub>COOH [9], H<sub>3</sub>BO<sub>3</sub> [10], BF<sub>3</sub>-H<sub>2</sub>O [11], 4-aminobenzenesulfonic acid [12], N-methyl-2-pyrrolidonium hydrogen sulphate [13], and short oligo ethylene glycolic dicationic [14]. Although the use of these catalysts are efficient,

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in some cases, homogenous catalysts have some limitations such as difficult to remove from the reaction mixture, unrecyclable, requiring tedious workup procedures for the elimination of transition metal contaminants from the synthesized product which thus causing a concern to ecological and economic issues [15-17]. These problems have led some researchers to focus on synthesizing 1,5-benzodiazepine and its derivatives through green chemical processes, i.e. performing the reaction under solvent-free condition and developing heterogeneous catalyst [15].

During the past few years, an extensive research has been devoted on the development of heterogeneous catalyst for organic transformations. Among the various heterogeneous catalyst, solid acid catalyst, such as: zeolites have gained tremendous attention due to their capability to accommodate acidity, high stability, inexpensive and abundance, non-corrosive and non-hazardous materials, and eco-friendliness availability [15,18]. Several types of zeolites have been used to synthesize 1,5-benzodiazepine derived compounds such as zeolite HY, H-ZSM, H-MCM-21, and heulandites [15,19,20]. Although the amount of natural zeolites is abundant, the utilization of such catalyst for the preparation of 1,5-benzodiazepine is still limited. Thus, it is highly desirable to study the catalytic activity of natural zeolite for the synthesis of 1,5-benzodiazepine.

In continuation of our work on the development of environmentally benign processes based on principles of green chemistry [21-24], herein we report the synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (Figure 1). To the best of our knowledge, the use of natural zeolite, especially Indonesian natural zeolite, as the catalyst for the cyclocondensation of 1,2-phenylenediamine and acetone under solvent-free condition has not been reported.

## 2. Materials and Methods

### 2.1 Materials and Instrumentations

The natural zeolite was collected from Klaten, Jawa Tengah, Indonesia. The reagents

used in this research were commercial products of high purity purchased from Merck, such as: 1,2-phenylenediamine (CAS number 95-54-5), acetone (CAS number 67-64-1), anhydrous Na<sub>2</sub>SO<sub>4</sub> (CAS number 7757-82-6), HCl 37% (CAS number 7647-01-0), and NH<sub>4</sub>Cl (CAS number 12125-02-9). Technical grade solvents were used directly without further purification.

Thin layer chromatography (TLC) was done on silica gel TLC-cards (layer thickness 0.20 mm, Merck) and visualized by exposure to UV Light. <sup>1</sup>H NMR spectra were recorded on Agilent V NMR spectrometer operating at 400 MHz using CDCl<sub>3</sub> as a solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, δ = 0.00 ppm). FTIR spectra were recorded on Prestige-21 spectrophotometer with KBr pellet. Melting point in °C was determined in open capillaries using electrothermal melting point apparatus Stuart MPS-10. X-ray diffraction (XRD) patterns were recorded using a Rigaku Miniflex 600 Benchtop X-Ray Diffraction operating at 450 W, 30 kV, and 15 mA, with graphite monochromator, scanning speed of 2° per minute. X-ray fluorescence (XRF) patterns were recorded using ED-XRF S2 Ranger Bruker operating at 50 W, 50 kV, and 2 mA.

### 2.2 Treatment of Natural Zeolite (TNZ)

The treatment of natural zeolite was done according to the method as described [25]. The obtained product was characterized using XRD, FTIR, and XRF which was then subjected as the catalyst for the synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine.

### 2.3 Synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine

In a 50 mL round bottom flask was added 1 mmol 1,2-phenylenediamine, 2 mmol acetone, and TNZ catalyst (15; 30; 45 and 60% wt/wt). Acetone (1 mmol) was added every 30 minutes until the total amount of acetone was 4 mmol. The reaction mixture was stirred at 50 °C. and the progress of the reaction was monitored using TLC until completion using hexane-ethyl acetate (7:3) as the eluent. The mixture was al-

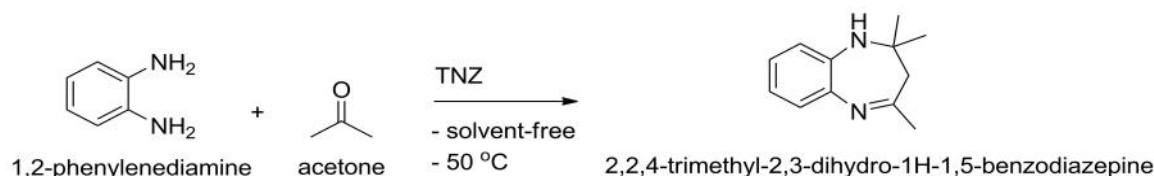


Figure 1. Synthetic Scheme of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine

lowed to cool at room temperature and 50 mL acetone was added. The resulting heterogeneous mixture was stirred for 2 h and filtered to remove the catalyst. The filtrate was dried using anhydrous Na<sub>2</sub>SO<sub>4</sub> to be followed by solvent removal. The obtained product was then recrystallized using n-hexane:ethyl acetate (7:3).

Data for 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine: yellow crystal (yield 73%), m.p. 134–135 °C (lit. 135–137 °C) [19]; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ in ppm): 1.35 (s, 6H), 2.27 (s, 2H), 2.43 (s, 3H), 6.74–7.27 (m, 4H); FTIR (KBr, ν<sub>max</sub> in cm<sup>-1</sup>): 3294, 2962, 1632, 1429. All spectral data are in good agreement with those of the literatures [19,31].

#### 2.4 Reusability Test of TNZ

The filtered TNZ catalyst which had been separated from the product was washed with 10 mL ethyl acetate, dried, and recovered. The recovery was done by washing the filtered TNZ with 10 mL acetone. The heterogeneous mixture was filtered and dried at 80 °C for 3 h. The TNZ catalyst was readily reused for the synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine. Under the same condition, TNZ was then reused for successive runs.

### 3. Results and Discussion

With the motivation to develop environmentally benign method based on green chemistry principles, i.e. use of catalytic chemical reaction and minimize use of solvent and toxic reactant, we decided to explore Indonesian natural zeolite as potential catalyst for the synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine under solvent-free condition. We initially tested the activity of natural zeolite directly for the condensation of 1,2-phenylenediamine and acetone. When performing the condensation both at room temperature (~ 28 °C) and 50 °C, no desired product was detected. Generally, natural zeolites are found with metal content contaminants (Mn<sup>+</sup>), such as: K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>3+</sup>, Fe<sup>3+</sup>, that could lower the purity level of zeolite. It also makes the presence of Brønsted acid sites possibly still covered by metals so that its activity as a catalyst is considered less. To overcome these problems, natural zeolite should be treated with an acid solution or an acid salt solution, such as: HCl, NH<sub>4</sub>Cl, or H<sub>2</sub>SO<sub>4</sub> at 50 °C [25-27].

In this research, treatment of natural zeolite was performed according to the reported procedure [25]. This was done by mixing of

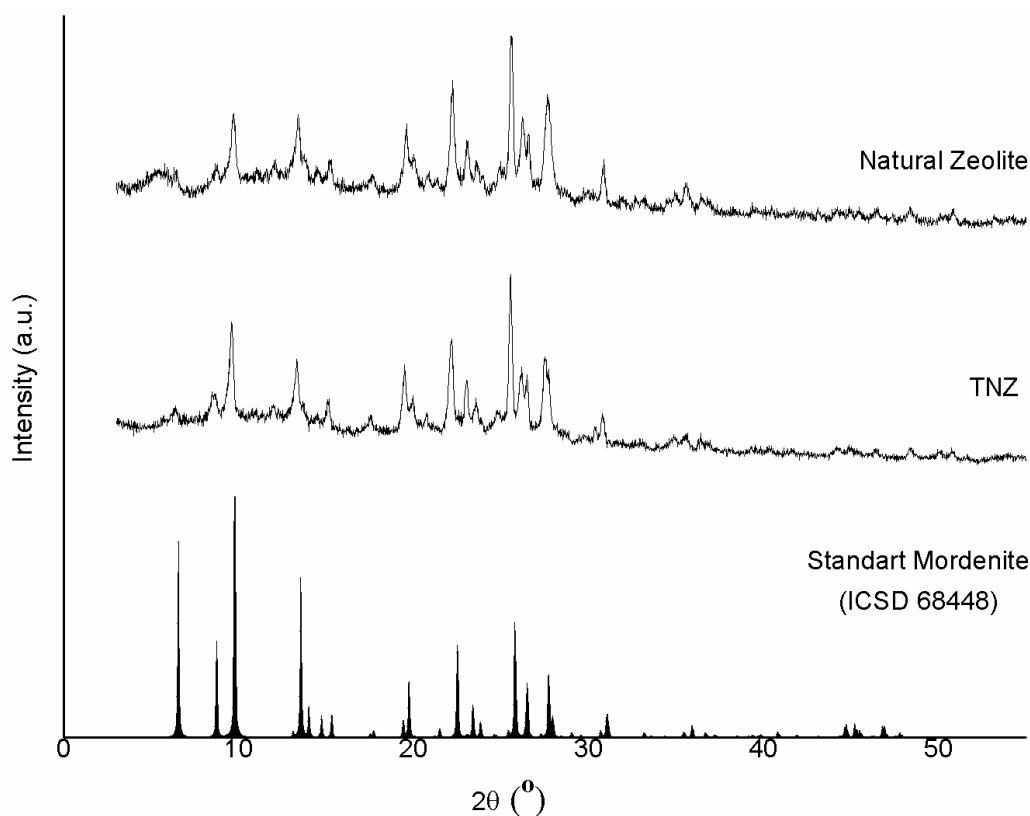


Figure 2. X-ray Diffraction Pattern of Natural Zeolite, TNZ, and Mordenite

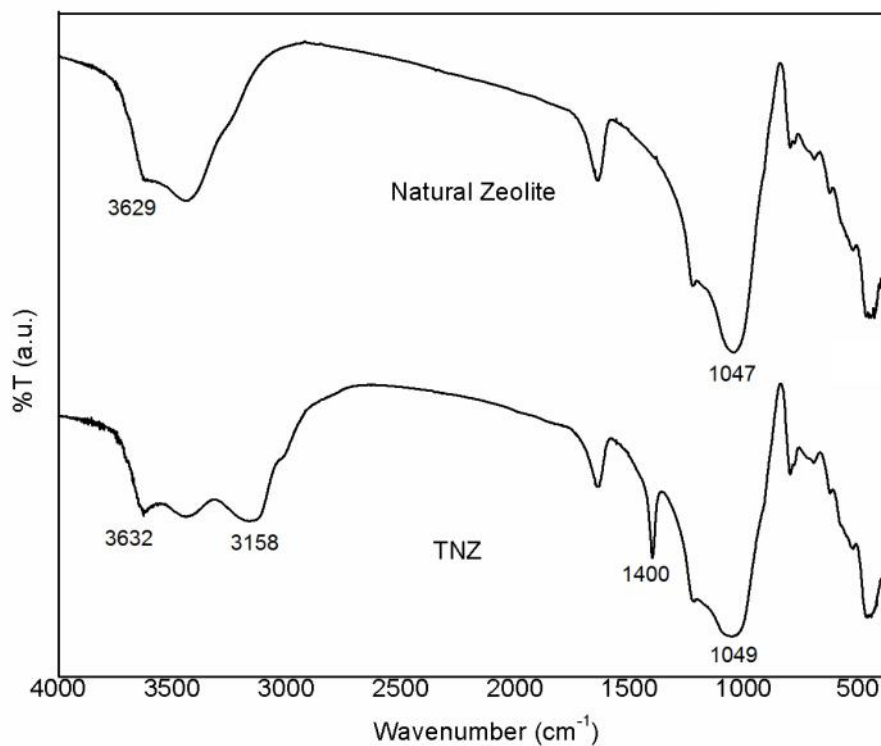


Figure 3. FTIR Spectra of Natural Zeolite and TNZ (KBr)

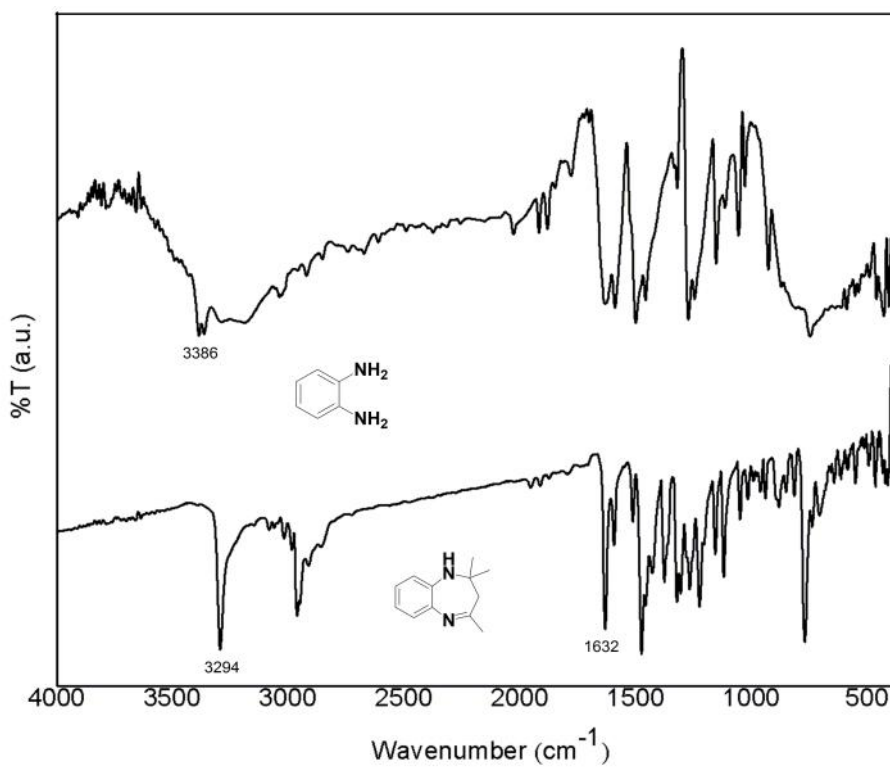


Figure 4. FTIR Spectra of 1,2-Phenylenediamine and the Cyclocondensation Product (KBr)

natural zeolite in hydrochloric acid solution that could afford decationation of  $Mn^{+}$  in the zeolite. In addition, by soaking natural zeolite in ammonium chloride solution for 5 days, the availability of  $NH_4^{+}$  ion could be expected to exchange the  $Mn^{+}$  metal cations of natural zeolite. Thus, the presence of  $NH_4^{+}$  ions on the zeolite surface might be able to provide an acid site which could activate the catalyst through its role in polarizing the carbonyl group on the ketone.

### 3.1 Characterization of TNZ

In order to study the character of the catalyst, several analyses, i.e. XRD, XRF, and FTIR, were performed. Characterization using XRD has been done to determine mineral content in natural zeolite after acid treatment based on diffractogram pattern compared with a reference. Based on XRD analyses (Figure 2), both the natural zeolite before and after treatment have a comparable pattern with the morденite type of zeolite (ICSD 68448) which are supported by the appearance of several major peaks at 2 theta i.e.  $9.75^{\circ}$  (hkl 200);  $13.10^{\circ}$  (hkl 220);  $19.38^{\circ}$  (hkl 311);  $22.47^{\circ}$  (150);  $25.45^{\circ}$  (hkl 202) and  $27.48^{\circ}$  (hkl 132).

Further characterizations of natural zeolite and TNZ have been done using XRF. Table 1 shows the metal contents of natural zeolite and TNZ. The results showed that after the treatment, there were a decrease on mineral contents in the zeolites, such as: Ca, Mg, Fe, and K. This indicated that after the treatment, several unwanted metal had been reduced. In this research, the Si/Al ratio of TNZ is 6.57 which can be relatively categorized as high Si/Al level in term of structure and acid stability [28].

To identify the functional group on the natural zeolite and TNZ, these materials were then analyzed using FTIR. FTIR results (Figure 3) showed that both natural zeolite and TNZ have absorption band at  $797\text{ cm}^{-1}$  indicating the

presence of symmetrical stretching vibration of Si–O–T (T = Si or Al) and absorption at  $1047$  and  $1049\text{ cm}^{-1}$  representing the existence of asymmetrical stretching vibration of Si–O–T. The absorption around  $3629\text{--}3632\text{ cm}^{-1}$  and  $1632\text{--}1634\text{ cm}^{-1}$  express the presence of Si–OH stretching vibration and Si–OH bending vibration, respectively. The appearances of these absorptions are appropriate to the functional group of zeolite [29]. Further analysis to the FTIR has been done to compare the difference absorption of natural zeolite and TNZ. Thus two new absorptions at  $1400$  and  $3158\text{ cm}^{-1}$  appear in FTIR spectra of TNZ which are typical vibrations for the existence of N–H group [30]. This indicates the presence of  $NH_4^{+}$  on the zeolite sites which might increase the acid strength of TNZ. High acidity is expected to provide great catalytic activity. Thus, we then tested the potency of TNZ as a catalyst for the condensation reaction between 1,2-phenylenediamine and acetone.

### 3.2 Synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine

The cyclocondensation reaction of 1,2-phenylenediamine and acetone was carried out using TNZ catalyst. Wherever possible, a chemical reaction is preferably performed without the use of solvent since organic solvent are frequently toxic and it is obvious that the waste generated from solvent is significant. Therefore, the condensation was performed under solvent-free condition. Initially, we started by studying the condensation without the use of catalyst at room temperature ( $\sim 28^{\circ}\text{C}$ ) and at  $50^{\circ}\text{C}$ .

The progress of the cyclocondensation was observed by TLC employing n-hexane : ethyl acetate = 7:3 as an eluent. The result showed that the reaction was not completed even after 8 h reaction time. With a way to improve the reaction, the TNZ was then tested on the condensation at  $50^{\circ}\text{C}$ . At first, a ratio of 1,2-phenylenediamine and acetone = 1:2 was used. However, by TLC analysis, the spot of the starting material was still presented even after 8 h reaction time which thus indicated that the reaction was not fully completed. To overcome this problem, 1 equivalent acetone was then added every 30 minutes until the total acetone reached 4 equivalent. Surprisingly, after 2 h reaction time, the starting materials have been fully converted. In addition, the effect of the catalyst loading on the condensation has been investigated. Weight ratio variation of TNZ, i.e. 15, 30, 45, and 60% (wt/wt) was examined.

**Table 1.** Composition of Elements in the Natural Zeolite and TNZ samples

No	Element	Composition (%)	
		Natural Zeolite	TNZ
1	Si	26.35	34.62
2	Al	4.99	5.38
3	Ca	4.99	2.11
4	Fe	3.86	2.97
5	Mg	1.67	0
6	K	1.93	1.27

The results showed that the highest yield of the reaction was obtained when the reaction time was 2 h using 30% of TNZ (see Table 2). Adding the quantity of the TNZ did not increase the yield even at prolonged reaction time indicating that the optimum catalyst loading and reaction time for this condensation are 30% and 2 h, respectively. In order to develop feasible experi-

**Table 2.** Optimization of TNZ catalyst loading on the synthesis of 2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine

Entry	Amount of catalyst (% wt/wt)	m.p. (°C)	Yield (%)
1	15	134-135	42
2	30	134-135	73
3	45	134-135	72
4	60	134-135	72

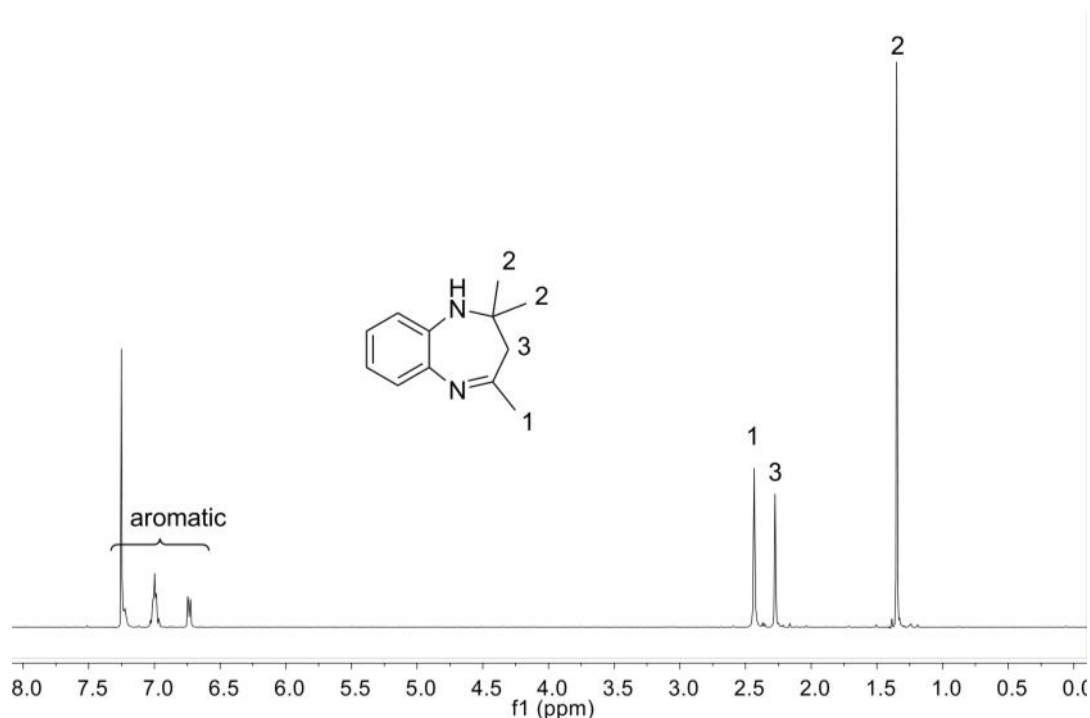
**Table 3.** Reusability of TNZ on the synthesis of 2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine

Run	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	5 <sup>th</sup>
Yield (%)	73	70	68	63	49

ments and to study the catalytic activity of TNZ relating with its reaction yield, repeated tests of the reaction were undertaken under the same experiment in optimum condition. Thus, similar outcomes (yield) were observed even after repeating the reaction three times.

Analysis of functional groups using FTIR on the product revealed the successful of the condensation (Figure 4). This was shown by the disappearance of two weak peaks around 3386  $\text{cm}^{-1}$  due to the primary amine absorption and the appearance of single absorption at 3294  $\text{cm}^{-1}$  confirming the presence of secondary amine group. Another strong evidence for the success of the cyclocondensation is the appearance of strong absorption at 1632  $\text{cm}^{-1}$  because of the imine ( $-\text{C}=\text{N}$ ) stretching vibration.

The accomplishment of the cyclocondensation can also be proved from the  $^1\text{H-NMR}$  spectrum. The  $^1\text{H}$  NMR spectrum (Figure 5) showed the proton signal of methyl group at  $\delta = 1.35$  ppm (6H, s), and 2.43 ppm (3H, s). While at  $\delta = 2.27$  ppm (2H, s) express the existence of a methylene group ( $-\text{CH}_2-$ ). The aromatic proton signals are appeared at  $\delta = 6.99$  ppm (2H, dd,  $J = 10.8$  Hz; 6 Hz, H-6) and 6.74–7.27 ppm. Both FTIR and  $^1\text{H}$  NMR analyses are confirmed the structure of the product, 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine, which are in a full accordance with those given in the literature [19,31].



**Figure 5.**  $^1\text{H}$  NMR Spectra of the cyclocondensation product of 1,2-phenylenediamine and acetone (400 MHz,  $\text{CDCl}_3$ )

One of the benefit applications of heterogeneous catalyst is its ability to be reused. This type of catalyst can be easily recovered after completion of the reaction in a straightforward manner, i.e. by filtration. In this research, the recovery of the TNZ catalyst was carried out by filtration, to be followed by washing with ethyl acetate and acetone to dissolve the organic compound trapped on the catalyst surface and dried at 80 °C for 3 h. The recyclability of TNZ was then examined for the condensation of 1,2-phenylenediamine and acetone under optimum condition and the results are presented in Table 3. The results showed that the TNZ can be recovered and is still effective to use for this cyclocondensation up to four times run without any significant activity loss.

#### 4. Conclusions

A simple and efficient approach has been developed for the synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine by cyclocondensation of 1,2-phenylenediamine and acetone in the presence of inexpensive catalyst TNZ under solvent-free condition in a good yield and short reaction time.

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