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ORIGINAL PAPER

Vitamin B_1 supported on alumina as an efficient heterogeneous catalyst for synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives

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Abstract The efficient synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives via four-component reaction of hydrazine hydrate, phthalic anhydride, aromatic aldehydes and barbituric acid using vitamin B_1 supported on alumina (VB_1-Al_2O_3) as a heterogeneous catalyst under thermal solvent-free conditions in excellent yields is described.

Keywords Hydrazine hydrate · Phthalic anhydride · Barbituric acid · Aldehyde · VB_1-Al_2O_3 · Catalyst

Introduction

Multicomponent reactions (MCRs) have been considered as a superior synthetic strategy for preparation of libraries of drug-like advanced compounds [1]. MCRs provide environmentally friendly processes by reducing the number of steps, energy consumption, and waste production [2].

Phthalazine derivatives have been shown to have many important biological properties such as vasorelaxant [3], anticonvulsant [4], cardiotonic [5], and many other pharmacological applications. Literature survey showed that three-component condensation reaction of phthalhydrazide, 1,3-diketone, and aldehydes to produce 2*H*-indazolo[1,2-b]phthalazine-triones [6, 7] but the only one synthetic method for preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-diones via three-component condensation from phthalhydrazide, barbituric acid, and arylaldehydes using $FeCl_3$ as catalyst was reported on the basis of central core of phthalazine [8]. In continuation of our researches in applications of reusable and green catalysts in organic reactions [9, 10], herein, we report a new and simple method for the synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives via four-component reaction of hydrazine hydrate, phthalic anhydride, aldehydes and barbituric acid in the presence of VB_1-Al_2O_3 as highly efficient and recyclable catalyst under solvent-free conditions (Scheme 1).

Experimental

All reagents were purchased from Merck or Aldrich and used without further purification. All yields refer to isolated products after purification. Vitamin B_1 supported on alumina (VB_1-Al_2O_3) as a heterogeneous catalyst was prepared according to the literature [11]. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Advance DPX 500 MHz instrument. The spectra were measured in DMSO-d_6 relative to tetramethylsilane. Infrared (IR) spectra were recorded using a JASCO FTIR 460 Plus spectrophotometer. Melting points were determined in open capillaries using a BUCHI 510 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates.

Preparation of vitamin B_1 supported on alumina [11]

VB_1-Al_2O_3 was prepared by mixing aluminum oxide (9 g, 90 active acidic, 0.063–0.200 mm) with a solution of VB_1 (1 g) in distilled water (15 mL). The suspension was stirred

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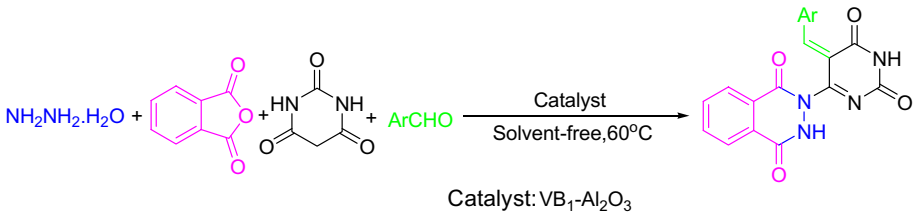
Scheme 1 Preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-diones



Scheme2 Preparation of VB_1-Al_2O_3

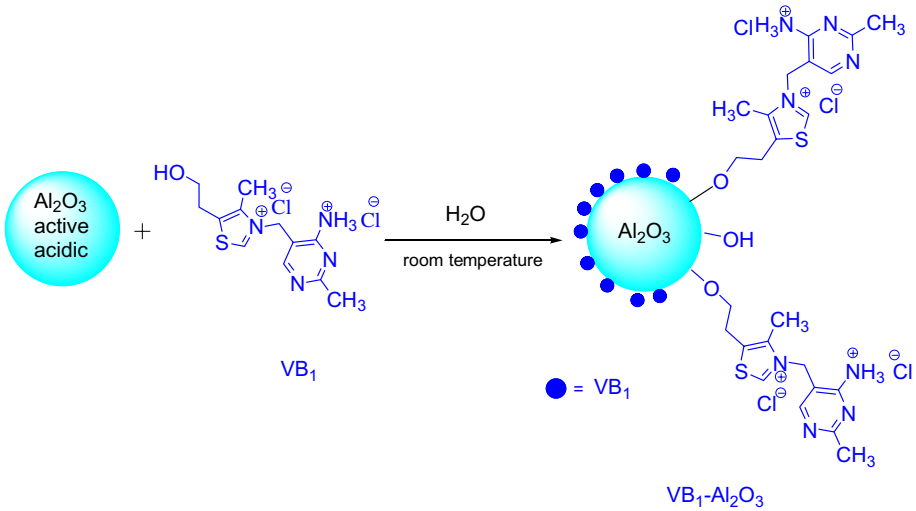
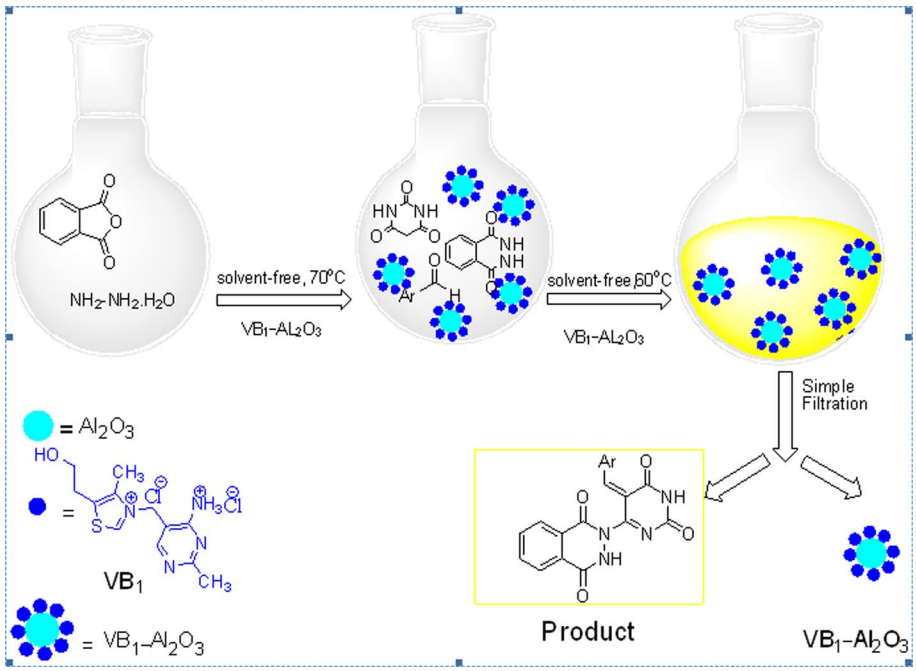


Fig. 1 preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione



for 1 h at room temperature, followed by removal of water in a rotary evaporator, and the solid powder was dried at 100 °C for 3 h in an oven and then cooled in a desiccators [11] (Scheme 2). Back titration analysis showed that 0.8 g of the catalyst is equivalent to 0.05 mmol H^+ per grams [11].

Typical procedure for the preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione

Hydrazine hydrate (1.2 mmol) and phthalic anhydride (1 mmol) were mixed at 70 °C until a white solid

phthalhydrazide was formed (10 min). Then, barbituric acid (1 mmol), benzaldehyde (1 mmol) and VB_1-Al_2O_3 (0.8 g, 5 mol %) was added to this solid-state mixture. The completion of reaction is monitored on TLC. After completion of reaction, the mixture cooled to room temperature. Then, EtOAc (30 mL) was added and the catalyst was recovered by simple filtration. The catalyst was washed with EtOAc and dried at 100 °C for 3 h, which could be reused without loss of its activity. The filtrate solution was concentrated and the solid product was recrystallized in EtOH to give pure products (Fig. 1).

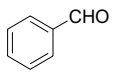
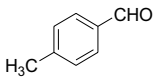
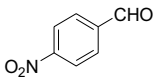
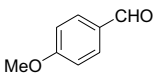
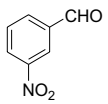
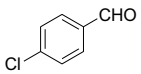
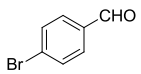
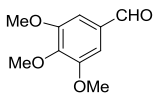
Selected spectroscopic data for one known compounds are given below

2-((13Z)-5-Benzylidene-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (*Table 1, entry 1*): yellow solid; Mp: 230–232 °C. IR (KBr, υ, cm^{-1}): 3390, 3017, 2853, 1761, 1657, 1639, 1596, 713, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.41 (s, 1H), 11.25 (s, 1H), 8.27 (s, 1H), 8.09–8.05 (m, 4H), 7.88–7.85 (m, 2H), 7.51–7.49 (m, 1H), 7.45–7.43 (m, 2H).

2-((13Z)-5-(4-Methylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3 dihydrophthalazine-1,4-dione (Table 1, entry 2): yellow solid; Mp: 258–260 °C. IR (KBr, υ, cm^{-1}): 3290, 3096, 2840,1749, 1665, 1621, 1581, 712, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.38 (s, 1H), 11.23 (s, 1H), 8.23 (s, 1H), 8.08–8.05 (m, 4H),7.88–7.85 (m, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 2.34 (s, 3H).

2-((13Z)-5-(4-Nitrobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3 dihydrophthalazine-1,4-dione (Table 1, entry 3): yellow solid; Mp: 274–276 °C. IR (KBr, υ, cm^{-1}): 3350, 3017, 2853, 1740, 1657, 1634, 1596, 717,

Table 1 Preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives via the four-component condensation reaction from hydrazine hydrate, phthalic anhydride, barbituric acid, and aromatic aldehydes using VB_1-Al_2O_3 as catalyst under thermal solvent-free conditions

Entry	Substrate	Time (min) / yield (%) [a]	Found m.p (°C) / L M.P (°C)[b]
1		12 / 91	230/230-232
2		10 / 92	259/258-261
3		13 / 89	274/274-276
4		11 / 90	255/256-258
5		10 / 92	231/232-234
6		11 / 91	256/255-257
7		14 / 88	280/280-282
8		10 / 91	262/ 262-264
9		12 / 91	271/270-272
10		10 / 92	270/268-270

[a] Yields refer to the isolated pure products

[b] Melting point of products was compared with literature [8]

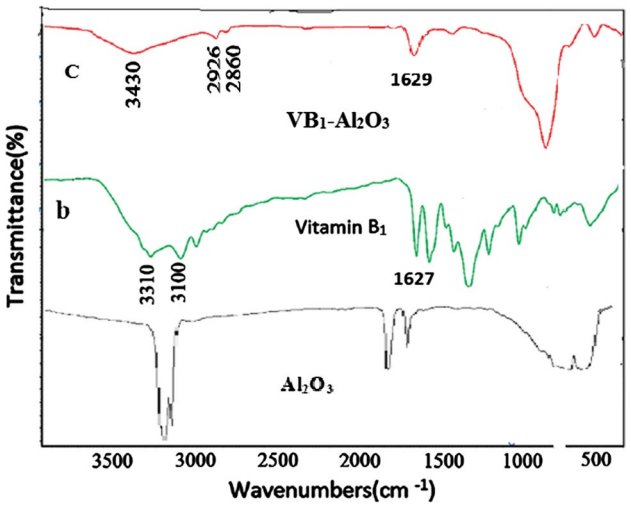


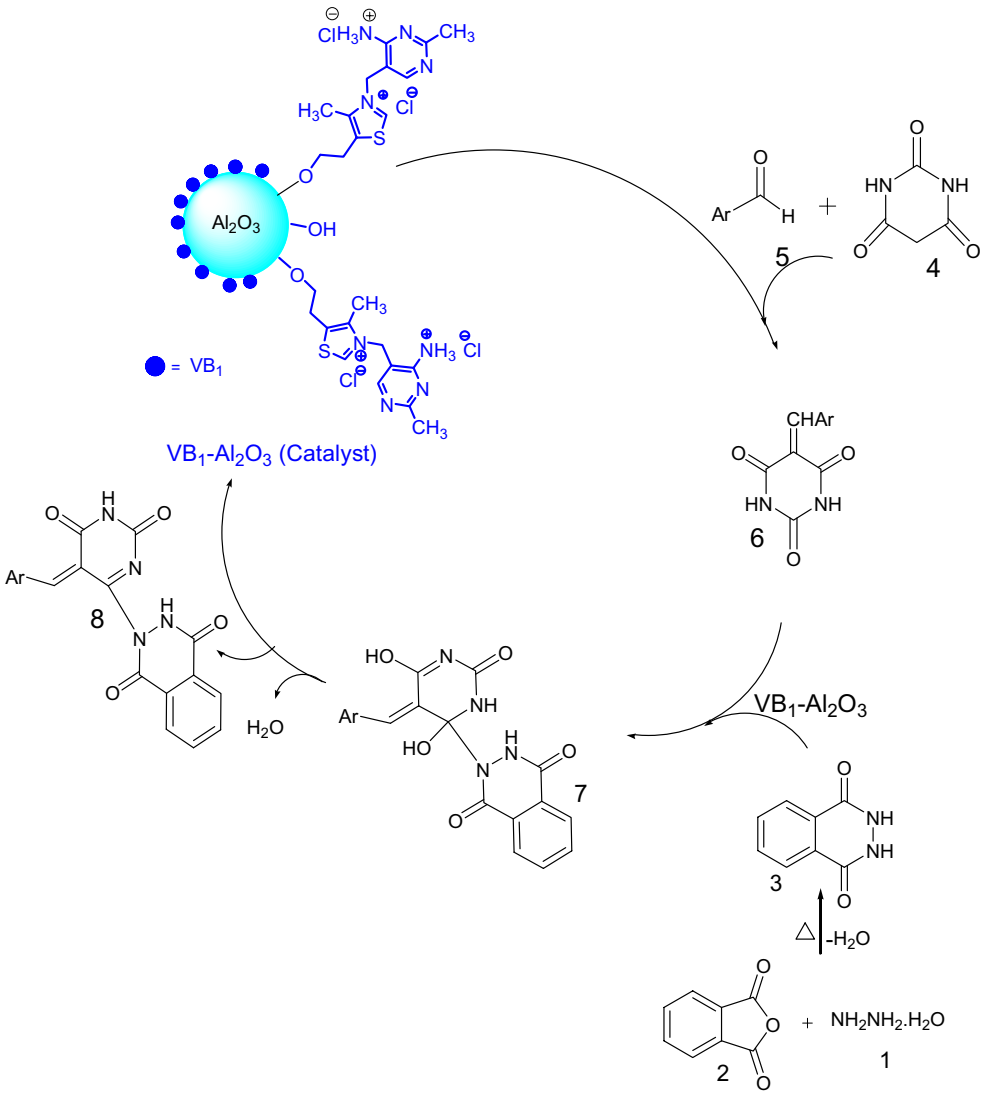
Fig. 2 FT-IR spectra of *a* Al_2O_3, *b* vitamin B_1, and *c* VB_1-Al_2O_3

^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.52 (s, 1H), 11.34 (s, 1H), 8.31 (s, 1H), 8.27–8.20 (m, 2H), 8.07–8.04 (m, 2H), 8.00 (d, J = 7.2 Hz, 2H), 7.87–7.83 (m, 2H).

2-((13Z)-5-(2-Methylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 4): yellow solid; Mp: 256–258 °C. IR (KBr, υ, cm^{-1}): 3452, 3314, 3070, 2959, 2872, 1691, 1615, 1569, 1226, 746, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.42 (s, 1H), 11.19 (s, 1H), 8.40 (s, 1H), 8.09–8.06 (m, 2H), 7.89–7.86 (m, 2H), 7.57 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 2.27 (s, 3H).

2-((13Z)-5-(3-Methylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 5): yellow solid; Mp: 232–234 °C. IR (KBr, υ, cm^{-1}): 3352, 3086, 2857, 1751, 1678, 1639, 1588, 709, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.40 (s, 1H),

Scheme 3 The proposed mechanism for the synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives



11.24 (s, 1H), 8.23 (s, 1H), 8.08–8.05 (m, 3H), 7.88–7.85 (m, 3H), 7.33 (d, $J = 7.2$ Hz, 2H), 2.31 (s, 3H).

2-((13Z)-5-(4-Methoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 6): yellow solid; Mp: 255–257 °C. IR (KBr, υ, cm^{-1}): 3370, 3042, 2847, 1745, 1693, 1646, 1545, 710, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm):11.31 (s, 1H), 11.18 (s, 1H), 8.36 (d, $J = 9.1$ Hz, 2H), 8.24 (s, 1H), 8.07–8.05 (m, 2H), 7.88–7.86 (m, 2H), 7.04 (d, $J = 8.8$ Hz, 2H), 3.86 (s, 3H).

2-((13Z)-5-(3-Nitrobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 7): yellow solid; Mp: 280–282 °C. IR (KBr, υ, cm^{-1}): 3300, 3056, 2831, 1726, 1670, 1689, 1598, 715, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.50 (s, 1H), 11.35 (s, 1H), 8.90 (s, 1H), 8.31–8.29 (m, 1H), 8.21 (d, $J = 7.6$ Hz, 1H), 8.07–8.05 (m, 2H), 7.89–7.85 (m, 3H), 7.72 (t, $J = 8.0$ Hz, 1H).

2-((13Z)-5-(4-Chlorobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 8): yellow solid; Mp: 262–264 °C. IR (KBr, υ, cm^{-1}): 3309, 3012, 2850, 1761, 1662, 1644, 1559, 718, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.42 (s, 1H), 11.21 (s, 1H), 8.24 (s, 1H), 8.07 (d, $J = 8.8$ Hz, 3H), 7.89–7.85 (m, 2H), 7.51 (d, $J = 8.4$ Hz, 3H).

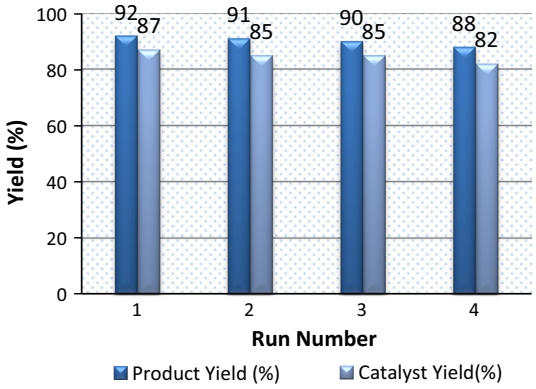


Fig. 3 Reusability of the catalyst in the reaction of 4-methylbenzaldehyde, barbituric acid and phthalic anhydride, hydrazine hydrate under solvent-free conditions (Table 1, Entry 2)

2-((13Z)-5-(4-Bromobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 9): yellow solid; Mp: 270–272 °C. IR (KBr, υ, cm^{-1}): 3203, 3092, 2850, 1726, 1660, 1654, 1598, 711, ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.42 (s, 1H), 11.28 (s, 1H), 8.21 (s, 1H), 8.07–8.04 (m, 2H), 7.97 (d, $J = 8.8$ Hz, 2H), 7.86 (dd, $J = 2.1$, 10.2 Hz, 2H), 7.66–7.62 (m, 2H).

*2-((13Z)-5-(3,4,5-Trimethoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (Table 1, entry 10):*yellow solid; Mp: 268–270 °C. IR (KBr, υ, cm^{-1}): 3370, 3042, 2847, 1744, 1690, 1646, 1578, 716,^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 11.37 (s, 1H), 11.24 (s, 1H), 8.25 (s, 1H), 8.07–8.05 (m, 2H), 7.89–7.86 (m, 2H), 7.83 (s, 2H), 3.81 (s, 6H), 3.78 (s, 3H).

Results and discussions

FT-IR analysis of VB_1-Al_2O_3

FT-IR spectra of Al_2O_3, vitamin B_1, and VB_1-Al_2O_3 are depicted in Fig. 2. The FT-IR spectrum of Al_2O_3 is well known, and its principal feature is a broad band between 950 and 500 cm^{-1}, ascribed to Al–O stretching. The surface of Al_2O_3 is covered by OH groups that cause water adsorption, and the band due to these species is between 3800 and 3000 cm^{-1}, centered at 3460 cm^{-1} [12]. In addition, this band is ascribed to OH stretching of the adsorbed water, the bridged hydroxyl group with molecular water, other OH groups, and isolated OH groups [13].The spectrum of supported VB1-Al_2O_3 (c) also shows small bands around 2900 cm^{-1} that are related to asymmetric and symmetric C–H stretching. The peaks located at 3440 cm^{-1} can be attributed to the N–H stretching and confirmed that vitamin B_1 (b) was tethered on an alumina surface through its hydroxyl group. In the spectrum (c), the peak at 1626 cm^{-1} can be ascribed to the C=N or C=C bands stretching frequency of vitamin B_1 supported on alumina.

The acidity of VB_1-Al_2O_3 was also confirmed by the back-titration method. Thus, triplicate of 1 g sample was added to 5 mL of 0.1 N NaOH solution. To ensure that

Table 2 Comparison results of VB_1-Al_2O_3 in the four-component synthesis with $FeCl_3$ in the three-component synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives

Entry	Catalyst (mol %)	Conditions	Time (min)	Yield (%) [References]
1	$FeCl_3$ (15 mol %)	Solvent-free, 60 °C three-component reactions	16–25	89–94 [8][a]
2	VB_1-Al_2O_3 (5 mol %)	Solvent-free, 60 °C four-component reactions	10–14	(88–92)[b] (present work)

[a] Three-component condensation from phthalhydrazide, barbituric acid, and arylaldehydes using $FeCl_3$ as catalyst was studied [8]

[b] Four-component reaction of hydrazine hydrate, phthalic anhydride, aldehydes and barbituric acid in the presence of VB_1-Al_2O_3 was studied

all of the VB_1-Al_2O_3 was reacted with NaOH, the mixture was sonicated for 10 min. To each vessel, two drops of phenolphthalein pH-indicator was added. Back-titration was accomplished by titrating the unreacted base in solution with standardized 0.1 N HCl solutions to the first permanent cloudy pink color. This was subtracted from the primary amount of base to find the amount of base that actually reacted with the VB_1-Al_2O_3 as an acid. The acidity value of VB_1-Al_2O_3 was obtained as 0.06 mmol g^{-1} by adding 4.4 mL of HCl. Our result was confirmed by the literature [8].

Total number of moles of NaOH added to the sample: 0.5 mmol, total volume of HCl added to each vessel: 4.4 mL (0.44 mmol), number of moles of NaOH that neutralize VB_1-Al_2O_3: 0.06 mmol (0.5–0.44 mmol).

To choose optimum conditions, first we tried to prepare tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione from the reaction of phthalic anhydride (1 mmol) and hydrazine hydrate (1.2 mmol), barbituric acid (1 mmol), benzaldehyde (1 mmol) as a model reaction in the presence of different catalytic amount of catalyst (1, 3, 5, 8, 10 mol %) at different temperatures (25, 40, 60, 70, 80 °C) under solvent-free conditions. The best results were obtained with 5 mol % of VB_1-Al_2O_3 at 60 °C. Using these optimized conditions, the scope and efficiency of these procedures were explored for the synthesis of a wide variety of substituted tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione. Interestingly, a variety of aldehydes including *ortho*-, *meta*-, and *para*-substituted aryl aldehydes participated well in this reaction and gave the tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives in excellent yield (Table 1). As seen from Table 1, both aromatic aldehydes carrying electron-withdrawing and electron-donating substituent act well in this reaction conditions.

According to the only one published paper [8], the proposed mechanism for the synthesis of the products is shown in Scheme 3. First, the reaction occurs via initial nucleophilic addition of hydrazine hydrate (1) to phthalic anhydride (2), followed by dehydration to obtain phthalhydrazide (3). The second step stared by Knoevenagel condensation of barbituric acid (4) and aldehyde (5) in the presence of catalyst follow to get the compound (6). After Michael addition of phthalhydrazide (3) at C=O bond of 6, cause to formation intermediate (7). Finally, the products (8) obtained by elimination of water molecule.

Recovery of the green catalyst is more important in a synthetic methodology. Thus, we investigated the reusability of VB_1-Al_2O_3 in the reaction. The recovered catalyst was reused for at least four runs without any loss of its activity (Fig. 3).

To show the accessibility of the four-component reaction of the present work in comparison results with only one catalyst ($FeCl_3$) which reported in the literature [8], we summarized some of the results for the preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives in Table 2. Table 2 shows that VB_1-Al_2O_3 is an efficient catalyst with respect to the reaction time and obtained yields relative to $FeCl_3$ as catalyst.

Conclusions

We have developed a practical and green strategy for the synthesis of tetrahydro-2,6- dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-diones using VB_1-Al_2O_3 as environmentally bingeing catalyst under solvent-free conditions. Clean reactions, short reaction times, high yields, reusability of the catalyst and easy workup are advantages of this protocol.

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