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# Metal-organic frameworks as efficient catalytic systems for the synthesis of 1,5-benzodiazepines from 1,2-phenylenediamine and ketones



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#### 1. Introduction

1,5-Benzodiazepine derivatives have received significant attention as compounds with biological activity [1]. 1,5-Benzodiazepine derivatives possess antifungal, antibacterial, antifeedant, antiinflammatory, analgesic and anticonvulsant activities. Moreover, 1,5-benzodiazepines are widely used as synthons for the synthesis of triazole [2,3] and oxadiazole derivatives [4,5]. The traditional approach for synthesis of 1,5-benzodiazepines is based on the acid-catalysed reaction of 1,2-phenylenediamine (I) with ketones. Various catalytic systems for this reaction have been reported in the literature, a great number of which have appeared only very recently [6-12]. Thus, synthesis of 1,5-benzodiazepines has been achieved using different homogeneous catalysts, such as ZnCl<sub>2</sub> YbCl<sub>3</sub> [11], BF<sub>3</sub>-etherate [13], and 1-butvl-3-[10]. methylimidazolium bromide (ionic liquid) [14]. As solid acid catalysts, polyphosphoric acid on SiO<sub>2</sub> [15], sulfated zirconia [7], polymer-supported FeCl<sub>3</sub> [12], H<sub>2</sub>SO<sub>4</sub>/SiO<sub>2</sub> [8], Amberlyst-15 [9], and zeolites [16,17] were used. Le et al. [18] suggested the use of

#### ABSTRACT

Benzodiazepines and their derivatives are a very important class of nitrogen-containing heterocyclic compounds with biological activity that are widely used in medicine. In this study, we demonstrated synthesis of 1,5-benzodiazepines from 1,2-phenylenediamine and ketones (acetone, cyclohexanone, acetophenone, methyl ethyl ketone) in the presence of isostructural porous metal-benzenetricarboxylates of the families MIL-100(M) (M: V<sup>3+</sup>, Al<sup>3+</sup>, Fe<sup>3+</sup> and Cr<sup>3+</sup>) and three porous aluminium trimesates Al-BTCs (MIL-96(Al), MIL-100(Al) and MIL-110(Al)). A combination of catalytic, theoretical and physicochemical methods showed that reaction rates and yields of 1,5-benzodiazepines were adjusted by the type of metal ions and accessibility of active sites. The yield of 1,5-benzodiazepines in the presence of MIL-100(M) was comparable with zeolites, such as HY, H-ZSM-5,  $\beta$ -zeolite and heulandite.

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metal-organic frameworks (MOFs), such as MOF-235(Fe), MOF-5 (Zn), Mn(BDC), MOF-199(Cu), and Ni<sub>2</sub>(BDC)<sub>2</sub>(DABCO), as heterogeneous catalysts for the cyclocondensation of acetone with different 1,2-diamines, including 1,2-phenylenediamine, 4-chloro-1,2-phenylenediamine, 4-bromo-1,2-phenylenediamine, and 4-methyl-1,2-phenylenediamine, to the corresponding 1,5benzodiazepines. It was found that MOF-235(Fe) was highly active compared with other studied MOFs. Unfortunately, the effects of the structure of MOFs and the nature of active sites in the frameworks of MOFs on the reaction rate and product distribution were not investigated.

During last few years, metal-organic frameworks have attracted significant interest as materials for catalytic applications due to their unique structure and physicochemical properties [19–21]. Of material importance is that a large variety of structural types and chemical compositions can be obtained by changing either the organic linker or the metal. A large specific surface area, homogeneous distribution and high accessibility of active sites for reactants also govern the catalytic properties of MOFs. The latest investigations note that the type of metal ions in the framework of MOFs affects their catalytic properties [22–24]. Thus, the effect of the metal ion on catalytic properties of the isostructural MOFs of the families MOF-74(Co, Cu, Mg, Ni) and MIL-100(Al, Cr, Sc, V) was investigated in reactions of 3,4-dihydro-2 H—pyran with



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alcohols [24]. It was found that the yield of tetrahydropyranyl ether decreased in the following orders:

MIL-100(V) > MIL-100(Sc) > MIL-100(Cr) > MIL-100(Al) MOF-74(Mg) > MOF-74(Ni) > MOF-74(Cu) > MOF-74(Co)

The main reasons for these trends are related to the accessibility and strength of open metal sites. The dependence of catalytic properties on the type of metal ions was also demonstrated for the isostructural MOFs of the families MIL-100(M) and MIL-53(M) (M = V, Al, Fe and Cr) and mixed MIL-53(Al,V) (Al/V – 100/0, 75/25, 50/50, 25/75 and 0/100 atom/atom) in the synthesis of solketal from acetone and glycerol (I) [23]. According to this investigation, glycerol conversion decreased in the following order V<sup>3+</sup> > Al<sup>3+</sup> > Fe<sup>3+</sup> > Cr<sup>3+</sup>, which was in agreement with the value of the zero point of charge of the surface (pH<sub>PZC</sub>). Reasonably, the type of metal ions in the framework of MOFs should also be important for the reaction between (I) and ketones.

As a part of a systematic study on the catalytic behaviour of MOFs and with a view to increase knowledge about the dependence of their catalytic properties on the type of metal ions, we report for the first time on variable catalytic activity of isostructural MOFs of the families MIL-100(M) (M: V<sup>3+</sup>, Al<sup>3+</sup>, Fe<sup>3+</sup>and  $Cr^{3+}$ ) and three porous aluminium trimesates Al-BTCs (MIL-96 (Al), MIL-100(Al) and MIL-110(Al)) in the cyclocondensation of (I) with acetone to 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiaze pine (1,5-benzodiazepine, (III)) (Scheme 1). We suggested that the type of metal ions in the MOFs should allow to adjust the catalytic activity of MIL-100(M). Moreover, three porous aluminium trimesates Al-BTCs are good candidates for our investigation because their textural properties are different, important for analysis of the effect of the amount of active sites and their accessibility to the reactants. Thus, the structure of MIL-96(Al)  $([Al_{12}O(OH)_{18}(H_2O)_3(Al_2(OH)_4)[BTC]_6 \cdot 24H_2O])$  has three types of cages. The pore-opening diameters of these cavities are in the range of 2.5–3.5 Å [25]. MIL-110(Al)  $(Al_8(OH)_{12}{(OH)_3(H_2O)_3})$ [BTC]<sub>3</sub>·42H<sub>2</sub>O) also has a honevcomb topology. MIL-110(Al)'s structure is built up from the connection of an octahedrally coordinated aluminium octameric unit through trimesate ligands delimiting one-dimensional, large hexagonal channels (16 Å) [26]. At the same time, mesoporous MIL-100(Al) ([Al<sub>3</sub>O(OH)(H<sub>2</sub>O)<sub>2</sub>[BTC]· 24H<sub>2</sub>O]) possesses a three-dimensional framework structure with two types of cavities [27,28]. The first type of cavity is delimited by 12 pentagonal windows with a size of 5.5 Å (dodecahedral cage); the second cavity is delimited by 12 pentagonal windows and 4 hexagonal windows with a size of 8.6 Å (hexadodecahedral

cage). The amount of Lewis acid sites (LAS) in MIL-100(M) and Al-BTCs was measured by EPR spectroscopy using the 2,2',6,6'-tet ramethyl-1-piperidinyoxyl radical (TEMPO) as the probe molecule. Earlier, we successfully used this technique in the analysis of coordinatively unsaturated sites (Al<sup>3+</sup><sub>CUS</sub>) in Al-BTCs, such as MIL-100(Al), MIL-96(Al) and MIL-110(Al) [22]. This method is based on the reaction of TEMPO with only one acid site [29-31]. According to this property, the maximum amount of radicals adsorbed (until the EPR spectrum of the TEMPO radical appears in the solution) corresponds to the concentration of acid sites. Analysis of the main factors that affect the reaction rate and the isomer selectivity was based on a combination of catalytic, theoretical and physicochemical methods. Another purpose of our investigation was to demonstrate the catalytic potential of the studied MOFs as heterogeneous catalysts for this reaction. To this end, we investigated cyclocondensation of (I) with other ketones, such as cyclohexanone, acetophenone and methyl ethyl ketone, to obtain the corresponding 1.5benzodiazepines.

#### 2. Experimental

#### 2.1. Materials

Commercial methanol, acetone (Acros Organics), 1,2phenylenediamine (Acros Organics), cyclohexanone (99+ %, Acros Organics), acetophenone (98%, Acros Organics), 2-butanone (99+ %, Acros Organics), 2,2',6,6'-tetramethyl-1-piperidinyoxyl radical (TEMPO) (Aldrich), Al(NO<sub>3</sub>)<sub>3</sub> 9H<sub>2</sub>O (98 wt%, Junsei), 1,3,5benzenetricarboxylic acid (H<sub>3</sub>BTC) and 1,3,5-trimethyl-benzenetri carboxylate (Me<sub>3</sub>-BTC, 98%, Aldrich), ortho-phosphoric acid (H<sub>3</sub>PO<sub>4</sub>, 85 wt%, Merck), sodium hydroxide (NaOH, 4 M), nitric acid (HNO<sub>3</sub>, 60 wt%), iron powder (Fe<sup>0</sup>, 99%, DC Chemical Co.), CrO<sub>3</sub> (98%, Junsei) and hydrofluoric acid (HF, 48%, OCI Company Ltd.) were used without any further purification. Beta zeolite (Si/Al 30, framework type BEA) and H-ZSM-5 (Si/Al 28, framework type MFI) were synthesized in a way similar to reported methods [16,32].

#### 2.2. Synthesis of metal-benzenetricarboxylates

Al-BTCs were synthesized from Al(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, 1,3,5benzenetricarboxylic acid (H<sub>3</sub>BTC) or trimethyl 1,3,5benzenetricarboxylate (Me<sub>3</sub>-BTC), sodium hydroxide (NaOH, 4 M), nitric acid (HNO<sub>3</sub>, 60%) and deionized water similar to the reported methods for MIL-100(Al) [27,28], MIL-110(Al) [27] and MIL-96(Al) [25] under autogenous pressure at 210 °C. The reactant compositions for the desired phases are shown in Table S1 (Sup-



Scheme 1. The cyclocondensation of 1,2-phenylenediamine with acetone.

porting Information (SI)). MIL-100(Fe) was synthesized according to a reported procedure [33]. MIL-100(Cr) was synthesized in a way similar to a reported method [34]. MIL-100(V) was synthesized in a way similar to a reported method [35]. The designation of the samples, chemical composition and textural data of samples are presented in Table 1 and Figs. S1–S2 (SI).

#### 2.3. Instrumental measurements

The porous structure of the materials was determined from the adsorption isotherm of N<sub>2</sub> at -196 °C using a Micromeritics ASAP 2400. The specific surface area (S<sub>BET</sub>) was calculated from the adsorption data over the relative pressure range between 0.05 and 0.20. The total pore volume (V<sub> $\Sigma$ </sub>) was calculated from the amount of nitrogen adsorbed at a relative pressure of 0.99. The X-ray diffraction patterns were measured on a X-ray diffractometer (ThermoARL) with Cu-K<sub> $\alpha$ </sub> ( $\lambda$  = 1.5418 Å) radiation.

#### 2.4. Lewis surface acidity investigation by EPR spectroscopy

All samples for EPR measurements were prepared using "break seal" techniques. For this, 0.015–0.020 g of sample (Al-BTC, MIL-100(Al), MIL-100(Cr)) was loaded into a quartz cell and evacuated at 200 °C until an absolute pressure of 20 mTorr was reached and maintained for 3 h. MIL-100(V) and MIL-100(Fe) were loaded into a quartz cell and calcinated at 200 °C in air for 3 h, and air was blown out with N<sub>2</sub>. After cooling to room temperature under vacuum conditions, 1 mL of  $3.2 \cdot 10^{-5}$ – $6.2 \cdot 10^{-4}$  M TEMPO in toluene was added to the sample. The EPR spectra were recorded at room temperature. The concentration of TEMPO was calculated after the calibration procedure (error ± 10%).

The EPR spectra were measured with an ERS-221 EPR spectrometer working in the X-band (v = 9.3 GHz). The EPR spectra were

#### Table 1

Textural properties of M-BTC materials.

recorded at 20 dB attenuation with a typical microwave power of 3 mW.

#### 2.5. Catalytic tests

The reaction of (I) with acetone was carried out at 30-50 °C in a jacketed glass reactor (10 mL) equipped with a magnetic stirrer and connected to thermostat. The temperature control was ±1 °C. Methanol was used as solvent. Before reaction, all catalysts were activated at 200 °C for 2 h in air in order to remove adsorbed water. The standard procedure was as follows: 0.1 mmol of (I), 4 mL of solvent (methanol, ethanol, acetonitrile or 1,2-dichloroethane), 2.5-4 mmol of acetone and 5-20 mg of catalyst were added into the reactor. At different time intervals, aliquots were taken from the reaction mixture and analysed by GC and GC-MS analysis (SI). A gas chromatograph (Agilent 7820) with a flame ionization detector and an HP-5 capillary column was used to analyse products quantitatively. *n*-Decane was used as the internal standard. The GC-MS analysis of the organic phase was performed with a GC-MS-QP2010 Ultra gas chromatography-mass spectrometer. Analysis conditions were as follows: GC: Injection port temperature 250 °C, capillary column GsBP1-MS 30 m  $\times$  0.32 mm, programmed heating: 50 °C (7.5 min)-20 °C/min-300 °C (10 min), and carrier gas – He (linear velocity of 50 cm/s); MS: Determined m/z 35–500, detector voltage 0.8 kV, emission current 60  $\mu$ A, and ion source temperature 250 °C.

#### 3. Results and discussion

#### 3.1. The choice of reaction medium

It is well-known [36,37] that in the presence of MOF-235, MOF-5, Mn(BDC), MOF-199, and Ni<sub>2</sub>(BDC)<sub>2</sub> (DABCO) the reaction rate and yield of (III) depend on solvent type. Therefore the effect of

	M content (wt.%)	Textural data			
		$S_{BET} (m^2/g)$	$V_{\Sigma}$ (cm <sup>3</sup> /g)	$V_{\mu} (cm^3/g)$	
MIL-100(V)	19.5	1628	0.82	0.34	
MIL-100(Fe)	24.3	1794	1.56	0.35	
MIL-100(Cr)	19.5	1653	0.91	0.35	
MIL-100(Al)	15.9	1486	0.70	0.38	
MIL-110(Al)	17.3	679	0.58	0.27	
MIL-96(Al)	17.6	315	0.14	0.13	

#### Table 2

Effect of solvent on reaction of 1,2-phenylenediamine with acetone in presence of MIL-100(V).<sup>a</sup>

Solvent	Relative polarity <sup>b</sup>	Time (min)	Conversion of (I) (%)	Selectivity (%)		
				(II)	(III)	(Other)
MIL-100(V)						
Methanol	0.672	10	87	19	77	4
		30	96	13	81	6
		70	100	5	93	2
Ethanol	0.654	30	37	69	21	10
		180	74	27	67	6
Acetonitrile	0.460	30	43	73	18	9
		180	64	67	25	8
1,2-Dichlorethane	0.269	60	29	82	3	15
		180	41	75	9	16
MIL-100(Al)						
Methanol	0.672	90	92	74	17	9
		180	100	4	92	4
Ethanol	0.654	180	63	69	20	11
Acetonitrile	0.460	180	33	79	5	16
1,2-Dichlorethane	0.269	180	15	84	3	13

<sup>a</sup> Reaction conditions: 0.1 mmol of (I), 0.25 mmol of acetone, 0.015 g of catalyst, 4 mL of solvent, 50 °C.

<sup>b</sup> Data are from Ref. [38].



**Scheme 2.** The interaction of alcohol with LAS of MIL-100(M) ( $\bigcirc$  – metal atom,  $\bullet$  – oxygen atom).

solvent on conversion of (I) and yield of (III) was investigated in the presence of MIL-100(V) and MIL-100(Al) at an acetone/(I) molar ratio of 2.5 and 50 °C. The main results are shown in Table 2 and Fig. S3 (SI). According to experimental data, the conversion of (I) and yield of (III) decreased with decreasing solvent polarity (relative polarity [38]) in the following order:

#### Methanol > Ethanol > Acetonitrile > 1,2-Dichloroethane

The maximal efficiency was observed in methanol with its large relative polarity (0.672). Most likely, the application of polar solvent affects the formation and the spatial arrangement and configuration of intermediates. Moreover, Vimont et al. [39] demonstrated that alcohols favour a change in the surface acidity of MIL-100(Cr) due to the formation of the Brønsted acid sites (BAS) (Scheme 2). Amount and strength of BAS decrease with an increase in the size of the alcohol. We can assume that similar BAS is formed due to the interaction of methanol and ethanol with LAS of MIL-100(V) and MIL-100(AI). Thus, methanol was preferred as a reaction medium for the investigations.

The reaction has heterogeneous character in the presence of MIL-100(M) samples in methanol as reaction medium. One can be seen from Fig. 1, the reaction does not proceed after catalyst separation from the reaction mixture.

#### 3.2. The effect of the metal ion on catalytic properties of MIL-100(M)

Effect of the type of metal ions on reaction rate and distribution product was investigated for MIL-100(M) (M = V, Al, Fe and Cr). The main results are presented in Table 3, Figs. 2–3 and S4 (SI). From the kinetic data, one can see that the reaction proceeds via two steps (Scheme 1). In the first step, reaction between (I) and acetone

leads to the formation of (II), which then reacts with the second molecule of acetone to give (III).

The yield of (III) depends on the type of metal and decreases in the following order (Fig. 3A, Table 3):

MIL-100(V) > MIL-100(Fe) > MIL-100(Cr) > MIL-100(Al).

This order can be explained both by impact of acidity and the complexing ability of active sites.

It is well-known that both Brønsted and Lewis acids can be used as catalysts for these reactions [4,7,9,13,16,17]. Since MIL-100(M) possesses both type acid sites, we considered their effects on the reaction rate and yield of (**III**).

**Effect of Brønsted acid sites (BAS).** The high activity of MIL-100(M) can be related to the Brønsted acidity, which is associated with the existence of structural M-OH groups and BAS formed by guest molecules (water, alcohols, etc.) adsorbed onto Lewis acid sites (Scheme 2) [40,41]. Previously, in the condensation of glycerol with acetone, we demonstrated that the activity of MIL-100(M) correlated with surface acidity, which was determined as zero point of charge of the surface (pH<sub>PZC</sub>) by the method of mass titration in aqueous solution [23]. According to these data, surface acidity decreases in the following order (pH<sub>PZC</sub> values):

$$MIL-100(V) (3.41) > MIL-100(Al) (3.95) > MIL-100(Fe) (4.11) > MIL-100(Cr) (4.41).$$

The comparison of orders of  $pH_{PZC}$  and activity of MIL-100(M) does not reveal clear trend in the cyclocondensation of (I) with acetone. In spite of the high surface acidity, the yield of (III) in the presence of MIL-100(Al) was lower as compared with MIL-100(Cr) and MIL-100(Fe) (Table 3).

Effect of Lewis acid sites (LAS). The amount of LAS in MIL-100 (M) was determined by a spin probe EPR spectroscopy using a bulky probe molecule, such as 2,2',6,6'-tetramethylpiperidine-1-o xyl (TEMPO). Typical EPR spectra of the TEMPO complex (3.18·10<sup>-4</sup> mol/L) before and after adsorption on MIL-100(Cr) and the TEMPO complex adsorbed on MIL-100(Al) (0.98 mmol/g and 0.05 mmol/g) are shown in Figs. S5–S6 (SI). The main results of the estimation of the amount of LAS in MIL-100(M) are given in Table 3. One can see from these data that the amount of LAS (Al<sup>3</sup><sub>CIS</sub>)



Fig. 1. The cyclocondensation of 1,2-phenylenediamine with acetone in the presence of MIL-100(V) and MIL-100(Al) (Experimental conditions: 4 mL of MeOH, 0.1 mmol of (I), 0.25 mmol of acetone, 0.010 g of catalyst).

### Table 3

Surface acidity	r and catalytic n	concretion of MIL 100/M	materials in reaction o	f 1 7 phonulons	diaming with acotone
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	Catalyst	pH <sub>PZC</sub> <sup>a</sup>	Amount of LAS <sup>b</sup>			Catalytic properties <sup>c</sup>	
			M <sub>total</sub> (mmol/g)	M <sup>3+</sup> <sub>CUS</sub> (mmol/g)	M <sup>3+</sup> <sub>CUS</sub> /M <sub>total</sub> (mol/mol)	Time (min)	Yield of (III) (%)
1	MIL-100(Al)	3.95	5.89	0.98	0.17	100	47
2	MIL-100(Cr)	4.41	3.75	2.64	0.70	100	69
3	MIL-100(Fe)	4.11	4.34	2.28	0.52	100	92
4	MIL-100(V)	3.41	3.84	2.44	0.63	70	93

<sup>a</sup> pH<sub>PZC</sub> - zero point of charge of the surface was estimated by the method of mass titration in aqueous solution [23].

<sup>b</sup> Amount of LAS in MIL-100(M) materials was determined by EPR spectroscopy using TEMPO as probe molecul.

<sup>c</sup> 0.1 mmol of (I), 0.25 mmol of acetone, 0.015 g of catalyst, 4 mL of MeOH, 50 °C.



Fig. 2. Kinetic curves of the cyclocondensation of (I) with acetone in the presence of MIL-100(V) and MIL-100(Al) (Experimental conditions: 4 mL of MeOH, 0.1 mmol of (I), 0.25 mmol of acetone, 0.015 g of catalyst, 50 °C).



**Fig. 3.** (A) Kinetic curve of yield of (**III**) in the cyclocondensation of (**I**) with acetone in the presence of MIL-100(M). (B) Correlations between Z/r and yield of (**III**). (Experimental conditions: 4 mL of MeOH, 0.1 mmol of (I), 0.25 mmol of acetone, 0.015 g of catalyst, 50 °C).

and  $(Cr_{CJS}^{3+})$  are 0.98 and 2.64 mmol/g for MIL-100(Al) and MIL-100 (Cr) calcined at 200 °C, respectively. These values are lower than that determined by IR spectroscopy using CO (2180–2220 cm<sup>-1</sup>) as the probe molecule (MIL-100(Al) approximately 1.7 mmol/g [41] and MIL-100(Cr) approximately 3.5 mmol/g [39,40]). The amount of

LAS in MIL-100(Fe) is 2.28 mmol/g, which is also lower in comparison with the value determined by CO adsorption [42]. Total amounts of  $Fe^{2+}/Fe_{CUS}^{3+}$  in MIL-100(Fe) calcinated at 150 and 250 °C were 1.94 and 3.66 mmol/g, respectively. We can suggest that these differences are related to the difference in the size of the probe molecule, which affects the accessibility of LAS. Interestingly, the amount of LAS in MIL-100(V) (2.44 mmol/g) determined by the spin probe method is close to that determined by  $CD_3CN$  adsorption (approximately 2.3 mmol/g) [24].

According to EPR data, the amount of LAS decreases in the order (Table 3):

$$MIL-100(Cr) > MIL-100(V) > MIL-100(Fe) > MIL-100(Al)$$

The catalytic properties of MIL-100(M) are slightly dependent on the amount of LAS. The low conversion of (I) and yield of (III) in the presence of MIL-100(Al) are not surprising due to the lower amount and accessibility of active sites for reactants as compared with other MIL-100(M).

It is well-known that MIL-100(M) possesses a very high affinity for S- and N-containing materials [43,44] that allows to the use of MOFs for their adsorptive removal. Most likely, this parameter can play a key role in reaction between (I) and acetone. According to the chemistry of coordination complexes [45], the bonding strength between the NH<sub>2</sub>-group of (I) and M<sup>3+</sup> ion, i.e., the complexing ability of M<sup>3+</sup> ion to NH<sub>2</sub>-groups in (I), should depend on the ionic potential  $\varphi = \frac{Z}{r}$ , where Z and r are charge and the radius of the metal ion, respectively. The radius of the metal ion decreases in the order [46]:

$$\begin{split} &V^{3+}(0.63\pm0.003~\text{\AA}) > \text{Fe}^{3+}(0.62\pm0.003~\text{\AA}) > \text{Cr}^{3+}(0.61\pm0.001~\text{\AA}) \\ &> \text{Al}^{3+}(0.52\pm0.005~\text{\AA}) \end{split}$$

The  $\varphi$  value increases in this order can point to the decreasing the strength of complexing. According to this trend, active sites formed by Al^{3+} in MIL-100(Al) should possess lower complexing ability to NH<sub>2</sub>-groups in (I) in compared with active sites formed



Scheme 3. Possible mechanism of the cyclocondensation of 1,2-phenylenediamines with acetone.

by  $V^{3+}$ ,  $Fe^{3+}$  and  $Cr^{3+}$ . One can see from Fig. 3B the yield of (III) decreases with increasing  $\phi$  value:

#### MIL-100(V) > MIL-100(Fe) > MIL-100(Cr) > MIL-100(Al)

The radius of metal ion and strength of interaction between metal ions and reactants are strongly important in terms of the reaction mechanism. The mechanism of benzodiazepine formation via condensation of 1,2-phenylenediamines with ketones was considered in [13,47-50]. We can suggest that both acetone and (I) coordinate on the LAS, simultaneously, and interaction of acetone with LAS leads to the activation of the carbonyl group (Scheme 3A). At the same time, the  $NH_2$ -groups of (I) attacks the carbonyl group of the acetone, giving intermediate **1**. Then, this intermediate can attack the carbonyl group of a second activated acetone molecule giving diimine, which after intramolecular imine enamine cyclization forms the seven-membered 1.5-benzodiazepine ring. Moreover, intermediate 1 can transform to dihydrobenzoimidazole (IIa) due to the inside cyclization. We can assume that the radius of the metal ion is one of the crucial parameters for the simultaneous coordination of acetone and (I). Active sites formed by V<sup>3+</sup> with its large radius ion are more preferable than that formed by Al<sup>3+</sup>.

#### 3.3. Effect of structure and Lewis acidity on catalytic properties of Al-BTCs

The effect of structure of M-BTCs and amount of LAS on reaction rate and yield of (**III**) was investigated in the presence of Al-BTCs, such as MIL-100(Al), MIL-110(Al) and MIL-96(Al). Application of identical precursor reactants and control of the pH of the starting mixture and/or the reaction time allow us to synthesize Al-BTCs having three different structures [26,27]. Earlier, we estimated concentration of LAS ( $Al_{CUS}^{3+}$ ) on the surface of these solids by the spin probe method, i.e., EPR spectroscopy using TEMPO as the probe molecule [22]. It was found that the amount of LAS ( $Al_{CUS}^{3+}$ ) in MIL-100(Al), MIL-110(Al) and MIL-96(Al) calcined at 200 °C are 0.98, 0.62 and 0.14 mmol/g, respectively. The differences in the amount of LAS are in agreement with differences in their structure and textural properties.

The catalytic properties of these materials were investigated at 60 °C at an acetone/(I) molar ratio of 2.5. The kinetic profiles in the presence of Al-BTCs are shown in Fig. S7 (SI). According to the experimental data, the activity of Al-BTCs decreases in the order (Fig. 4)

#### MIL-100(Al) > MIL-110(Al) > MIL-96(Al)

This order is proportional to the total amount of LAS (Fig. 4). The larger the amount of LAS, the higher the yield of (III). Another explanation for this trend can be the difference in their structures. The large cavities and channels in the MIL-100(Al) structure ensure the free access to active sites for reagent molecules, which leads to an increase in the reaction rate.

Most likely, the distribution of LAS in the structure of Al-BTCs can also affect their activity. This effect can be estimated from the difference in TON calculated using Eq. (1):

$$TON = \frac{\Delta(III)}{N_{LAS}}$$
(1)

where  $\Delta$ (III) is the amount of (III) (mmol), N<sub>LAS</sub> is the amount of LAS (mmol). According to experimental data, the efficiency of Al-BTCs for the first of 10 min decreases in the order (TON):

MIL-110(Al) (7.3) > MIL-100(Al) (5.4) >> MIL-96(Al) (2.2)

This result notes that active sites (LAS) of MIL-110(Al) are located on the surface and their density is higher as compared with MIL-100(Al). The low activity of MIL-96(Al) can be related to high microporosity (Table 1) that affects the accessibility of the active sites for the reactants.

## 3.4. The catalytic properties of MIL-100(M) under solvent free conditions

Catalytic properties of MIL-100(M) were also investigated in the reaction of (I) with acetone at a 4/1 M ratio of acetone/(I) and 50 °C under solvent free conditions. The results given in Table 4 show

#### Table 4

Reaction of 1,2-phenylenediamine with acetone in presence of different catalytic systems under solvent-free conditions.<sup>a</sup>

	Catalyst	Time (min)	Yield of (III) (%)
1	MIL-100(V)	180 (300)	85 (95)
2	MIL-100(Fe)	180 (300)	76 (88)
3	MIL-100(Cr)	180 (300)	72 (81)
4	MIL-100(Al)	180 (300)	68 (75)
5	HY [16]	180	82
6	Heulandite [16]	300	81
7	Beta Zeolite	300	39
8	H-ZSM-5	300	32
	H-ZSM-5 [16]	420	52
10	1.7%Fe-MMM [51]	300	86
11	6.5%Fe-VSB-5 [51]	300	64

<sup>a</sup> 0.1 mmol of (I), 0.4 mmol of acetone, 0.02 g of catalyst, 50 °C.



Fig. 4. Kinetic curves of yield of (III) and correlation between amount of LAS and yield of (III) for 60 min in the cyclocondensation of (I) with acetone in the presence of Al-BTCs. (Experimental conditions: 4 mL of MeOH, 0.1 mmol of (I), 0.25 mmol of acetone, 0.015 g of catalyst, 60 °C.)



	Ketone	Gas basicity <sup>b</sup> (kJ/mol)	Product	Catalyst	Time (min)	Yield (%)
1	0	782.1		MIL-100(V) MIL-100(AI)	70 180	93 92
2		795.5		MIL-100(V) MIL-100(Al)	180 300	89 <sup>c</sup> 79 <sup>c</sup>
3	O II	829.3		MIL-100(V)	180	49 (68) <sup>d</sup>
4		811.2		MIL-100(V)	180	69 (82) <sup>d</sup>

<sup>a</sup> Reaction conditions: 0.1 mmol of (I), 0.25 mmol of ketone, 0.015 g of catalyst, 4 mL of MeOH, 50 °C.

<sup>b</sup> Data are from Ref. [52].

<sup>c</sup> Overall yield by two isomers.

<sup>d</sup> 60 °C.

that yield of (III) is adjusted by the nature of the metal ion. The maximal yield of (III) was observed in the presence of MIL-100 (V). In the presence of MIL-100(V), yields of (III) were 85 and 95% after 3 and 5 h, respectively (Table 4, run 1). The comparison of the catalytic properties of MIL-100(M) with that of zeolites reported in the literature [16] notes that the activity of MIL-100 (V) is comparable to that of zeolite HY (Si/Al 2.5, framework type FAU) (Table 4, runs 1 and 5). At the same time, zeolites such as zeolite heulandite (Si/Al 5, framework type HEU), H-ZSM-5 (Si/Al 28, framework type MFI) and  $\beta$ -zeolite (Si/Al 30, framework type BEA), show lower activity than MIL-100(V) (Table 4, runs 1, 6-9), which probably can be explained by the difference in surface acidity. Moreover, the low activity of zeolites can also be related to their high microporosity. Mesoporosity and the unique structure of MIL-100(M) are major parameters that likely affect their catalytic properties. Thus, the activity of MIL-100(Fe) is comparable with that of Fe-containing mesoporous mesophase silica material (1.7%Fe-MMM) [51] (Table 4, runs 2 and 10) and is strongly higher than that of Fe-containing microporous nickel phosphate molecular sieves (6.5%Fe-VSB-5) (Table 4, runs 2 and 11).

Noteworthy that in the presence of MIL-100(M) (M-Al, Cr, Fe) the yields of (**III**) under solvent free conditions were slightly different from those in methanol solvent (Tables 3–4). This phenomenon can be related to the formation of BAS due the interaction of methanol with LAS of MIL-100(M). These sites may contribute as active sites for the activation of carbonyl group of the acetone (Scheme 3B, step 1) which then reacts with the amine group of (**I**).

#### 3.5. Synthesis of different 1,5-benzodiazepines

The catalytic activity of the most active MIL-100(V) was investigated in the condensation of (I) with other ketones (cyclohexanone, acetophenone, ethyl methyl ketone). Similarly, for these ketones, we used excess amounts (ketone/(I), 2.5/1.0) in the reaction mixture and methanol as solvent. One can see from Table 5 that reaction of (I) with ethyl methyl ketone gave the corresponding 1,5-benzodiazepines (two isomers) in 89% overall yield at 50 °C for 180 min. Note that the corresponding 1,5-benzodiazepines (two isomers) also can be obtained in the presence of MIL-100 (Al). Their overall yield was 79% after 300 min. At the same time



Fig. 5. Recycling test in cyclocondensation of (I) with acetone in the presence of MIL-100(V) and MIL-100(Al) (Experimental conditions: (A) - 40 mL of MeOH, 1 mmol of (I), 2.5 mmol of acetone, 0.100 g of MIL-100(V), 30 °C, 60 min; (B) - 40 mL of MeOH, 1 mmol of (I), 2.5 mmol of acetone, 0.150 g of MIL-100(Al), 50 °C, 300 min). The amount of the reactants was corrected based on reaction conditions.

in the presence of MIL-100(V) the high yield of 1,5benzodiazepines from cyclohexanone and acetophenone were obtained at 60 °C for 180 min. In the reaction mixtures of (I) with ethyl methyl ketone and cyclohexanone, we observed also the corresponding diimines as minor products. It can be assumed that, since the imine formation reaction is in equilibrium, these products are subsequently converted to the desired 1,5-diazepines. Basicities (gas basicity [52]) of studied ketones are different one another (Table 5), which can be important for their activation on active sites (BAS) and water removal (Scheme 3B). Results in Table 5 show that gas basicity affects the yield of 1,5-benzodiazepines. The higher gas basicity, the lower yield of 1,5-benzodiazepines.

#### 3.6. Stability of MIL-100(M): Recycling test

Stability of catalysts in the reaction mixture is the important property for their application. The stability of high-active MII-100(V) and low-active MIL-100(Al) samples was investigated by means of recycling tests at an acetone/(I) molar ratio of 2.5 in methanol medium. After each catalytic test, the sample was separated from the reaction mixture by filtration, washed with acetone and used in the next cycles.

It was found that MIL-100(Al) can be used repeatedly without significant loss in catalytic activity during at least 6 catalytic cycles (Fig. 5). The yield of (III) was 81–86% in each cycle. According to the XRD data, structure of MIL-100(Al) after 6 cycles is not much different from that of fresh sample (Fig. S8, SI). The yield of (III) also does not change during 3 catalytic cycles (78-80%) in the presence of MIL-100(V). However, XRD patterns of the fresh MIL-100(V) and MIL-100(V) after first cycle are different each other (Fig. S8, SI), i.e. MIL-100(V) is not very stable under the reaction conditions. Probably, the high efficiency of MIL-100(V) might be related to the structure transformation, which needs further study.

#### 4. Conclusions

The catalytic behaviour of isostructural MOFs of the families MIL-100(M) (M:  $V^{3+}$ ,  $Al^{3+}$ ,  $Fe^{3+}$  and  $Cr^{3+}$ ) and three porous aluminium trimesates Al-BTCs (MIL-96(Al), MIL-100(Al) and MIL-110(Al)) was investigated in the cyclocondensation of (I) with acetone to provide 1,5-benzodiazepine. Reactions were carried out at 50 °C with an acetone/(I) molar ratio of 2.5 and 4.0 in different solvents (methanol, ethanol, acetonitrile, 1,2-dichloroethane) and under solvent free conditions. It was found that yield of 1,5benzodiazepine decreases with decreasing solvent polarity. The maximal yield of 1,5-benzodiazepine was observed in methanol, a solvent with large relative polarity.

The type of metal ions in the framework of MIL-100(M) affects the reaction rate and yield of 1,5-benzodiazepine. The yield of 1,5benzodiazepine decreased in the order:

MIL-100(V) > MIL-100(Fe) > MIL-100(Cr) > MIL-100(Al)

This order does not correlate with amount of LAS, which was determined by EPR spectroscopy using TEMPO as the probe molecule. Moreover, this trend does not agree with surface acidity, i.e., zero point of charge of the surface (pH<sub>PZC</sub>), which was determined by method of mass titration in aqueous solution. At the same time, the reaction rate and yield of 1,5-benzodiazepine correlated with the complexing ability of the  $M^{3+}$  ion to  $NH_2$ -groups in (I) that was estimated in terms of ionic potential  $\varphi = \frac{Z}{z}$ . The increasing  $\phi$ value leads to the decreasing complexing ability and, therefore, the decreasing yield of 1,5-benzodiazepine.

In the presence of Al-BTCs, the reaction rate and yield of 1,5-benzodiazepine were in agreement with the amount of LAS and decreased in the order:

MIL-100(Al) > MIL-110(Al) > MIL-96(Al).

The accessibility of active sites for the reactants was also important for reactivity of Al-BTCs.

Synthesis of other 1,5-benzodiazepines from (I) and cyclohexanone, acetophenone and ethyl methyl ketone in the presence of MIL-100(V) and MIL-100(Al) was also demonstrated. Gas basicity of ketones affects the yield of 1,5-benzodiazepines. The higher gas basicity, the lower yield of 1,5-benzodiazepines.

The efficiencies of MIL-100(V) and MIL-100(Fe) were compared with that of zeolites and zeotype materials reported in the literature. It was found that activity of MIL-100(V) is comparable to that of HY, while the activities of H-ZSM-5, β-zeolite and zeolite heulandite were much lower than MIL-100(V) or HY. At the same time, the activities of MIL-100(Fe) and mesoporous mesophase silica material 1.7%Fe-MMM were similar to each other, while the activity of microporous 6.5%Fe-VSB-5 was low.

Recycling experiments point that yield of (III) does not change during at least three and six catalytic cycles for MIL-100(V) and MIL-100(Al), respectively. According to XRD data, structure of MIL-100(Al) was stable for cyclic test, while the structure transformation of MIL-100(V) was observed after the first cycle.

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#### Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2017.08.009.

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