Catalysis Today 142 (2009) 303–307

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

The possible use of alkali metal modified NbMCM-41 in the synthesis of 1,4-dihydropyridine intermediates

Zuzanna Zienkiewicz [a,b], Vanesa Calvino-Casilda [a,b], Izabela Sobczak [a], Maria Ziolek [a], Rosa M. Martín-Aranda [b,*], Antonio J. López-Peinado [b]

[a] *Adam Mickiewicz University, Faculty of Chemistry, Grunwaldzka 6, 60-780 Poznań, Poland*
[b] *Departamento de Química Inorgánica y Química Técnica, Universidad Nacional de Educación a Distancia, C/ Senda del Rey 9, 28040 Madrid, Spain*

ARTICLE INFO

Article history:
Available online 6 December 2008

Keywords:
Alkali metal modified niobosilicate
NbMCM-41
Acetonylacetone cyclisation
Knoevenagel condensation
1,4-Dihydropyridines

ABSTRACT

In this work we have prepared the catalysts containing all alkali metals (from Li to Cs) supported on mesoporous niobosilicate molecular sieve, NbMCM-41, and for comparison also loaded on silicate MCM-41. The materials were characterised by N_2 adsorption, XRD, and test reactions (acetonylacetone cyclisation and Knoevenagel condensation). It has been found that niobium located in the mesoporous material plays a role of structural promoter which prevents the solid from the disordering caused by the treatment with alkali metal solution. Moreover, it changes the catalytic properties of basic centres generated by alkali metal loading in relation to those observed for alkali metals supported on silicate MCM-41. Rb/NbMCM-41 has been proposed as active and selective catalyst in the condensation of benzaldehyde and different substituted benzaldehydes with ethyl acetoacetate towards the synthesis of intermediates in the preparation of some dihydropyridines.

1. Introduction

Nowadays the increasing social and environmental pressure on industry to substitute traditional homogeneous-catalysed reactions by environmentally friendly technologies represents the most important driving force for the development of heterogeneous catalysis. Indeed, the solid catalysts have many advantages. They are non-corrosive and environmentally benign, presenting fewer disposal problems. Their reuse is possible and their separation from liquid products is much easier. Moreover, they can be designed to give higher activity, selectivity and longer catalyst life [1,2].

Heterogeneous catalysts containing basic active centres are one of the most important groups of solids applied in the liquid phase processes. Different reactions have been studied on solid bases like isomerization of linear butenes, aldolic condensation, and side chain alkylation in alkylaromatics. The Knoevenagel condensation has been also widely studied and used to measure the strength of the basic sites [3]. It is one of the most important C–C bonds forming reaction used in the synthesis of intermediates or end products for perfumes, pharmaceuticals and calcium antagonists and polymers [4]. In recent years, effort has been focused on the search for new solid bases for Knoevenagel condensation. In this work we have prepared the catalysts containing all alkali metals (from Li to Cs) located in the niobosilicate NbMCM-41 material, which appeared to be active in Knoevenagel condensation to prepare intermediates of 1,4-dihydropiridines derivatives (Scheme 1).

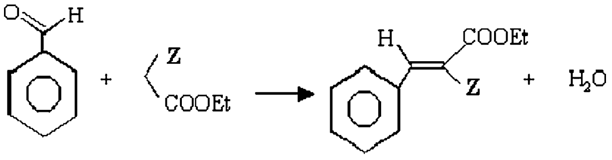
Dihydropyridines chemistry is of interest not only from the point of view of fundamental research on heterocyclic compounds [5], but especially because of expanding practical applications of 1,4-dihydropyridine derivatives (nifendipine, nitrendipine, and nicardipine) as pharmaceuticals in the line of calcium channel blockers [6]. There are two general approaches which involve variants of the Hantzsch reaction [7] for the preparation of 4-aryl-1,4-dihydropyridine derivatives. The route generally used, involves the reaction of an alkyl benzylindenacetatoacetate (1) with an alkyl β-aminocrotonate (2), and seems to afford the highest yields and the easiest purification (Scheme 2).

In this work, we have employed the Knoevenagel condensation (Scheme 1) and the acetonylacetone cyclisation (Scheme 2) as probe reactions to characterize the alkali metal modified NBMCM-41 catalysts. The Knoevenagel condensation catalysed by alkali modified NbMCM-41 was also employed to prepare compounds of the type (1), which are intermediates in the preparation of some dihydropyridines of type (3) (Scheme 3). A choice of NbMCM-41 matrix for the alkali metals was dictated by its higher stability under alkali medium conditions than that of silicate samples [8].

---

* Corresponding author.
E-mail address: rmartin@ccia.uned.es (R.M. Martín-Aranda).

0920-5861/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2008.10.022



Scheme 1. Knoevenagel condensation of benzaldehyde with malonic esters of different pK_a (ethyl cyanoacetate, ethyl acetoacetate, diethyl malonate and ethyl bromoacetate). Z = CN, $COCH_3$ and COOEt groups.

2. Experimental

2.1. Catalysts preparation and characterization

MCM-41 mesoporous molecular sieves were synthesized by a hydrothermal method [9] and modified to prepare NbMCM-41 according to the procedure described in Ref. [10]. Sodium silicate (27% SiO_2 in 14% NaOH; Aldrich) was used as a silicon source and cetyltrimethylammonium chloride (Aldrich) was applied as a surfactant. For the preparation of NbMCM-41 catalyst Nb(V) oxalate (CBMM, Brazil) was a source of Nb (Si/Nb molar ratio = 64 as assumed). The components were added in the following order: sodium silicate, surfactant, Nb(V) oxalate dissolved in oxalic acid. The formed gel was stirred for about 0.5 h. The pH was decreased from 12.5 to 11 with H_2SO_4 (MCM-41) or oxalic acid (NbMCM-41), after which the distilled water was added. The gel was loaded into a stoppered polypropylene (PP) bottle and heated without stirring at 373 K for 24 h. The mixture was then cooled down to room temperature and the pH level was adjusted to 11 with H_2SO_4 or oxalic acid. This reaction mixture was heated again to 373 K for 24 h to produce highly ordered samples. The resulting precipitated product was washed with distilled water, dried in the air at ambient temperature, and the template in the catalysts was removed by calcination at 823 K, 2 h in helium flow and 14 h in the air under static conditions.

The supports were impregnated by the incipient wetness impregnation with aqueous solution of $MeCH_3COO$ (Me = Li, Na, K, Rb, and Cs) and calcined at 723 K. The amount of alkali metal acetate used for the impregnation was calculated for the loading of metal equal to 0.5 mmol per 1 g of the support. The impregnated powder was dried at 373 K for 18 h and then calcined at 723 K for 10 h in an oven.

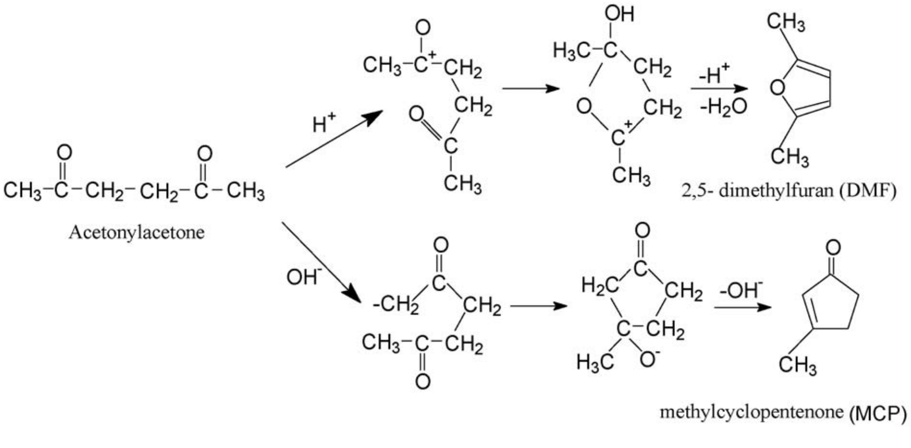
The prepared materials were characterised by nitrogen adsorption/desorption and XRD.

Nitrogen adsorption isotherms were measured at 77 K in the range of relative pressures from 10^{-6} to 0.995 using a Micromeritics ASAP equipment, model 2010. Prior to adsorption measurements, the samples were outgassed under vacuum at 573 K for 3 h in the port of the adsorption analyzer. The surface area was calculated by the BET method. The single point pore volume [11] was estimated from the amount adsorbed at a relative pressure of $\sim$0.97. The pore size distribution was calculated from nitrogen adsorption isotherms using the Kruk, Jaroniec and Sayari (KJS) method, which employs the classical Barret, Joyner and Halenda (BJH) algorithm [12] that describes the relation between the capillary condensation pressure and the pore diameter established for cylindrical mesopores by Kruk et al. [13–16].

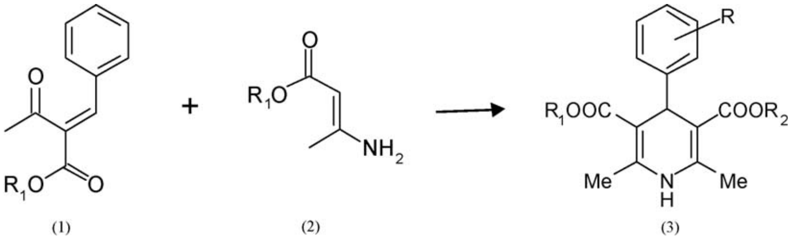
The XRD measurements were carried out with a Seifert C-3000 diffractometer with Cu Kα radiation (λ = 0.154 nm).

2.2. Acetonylacetone cyclisation

The materials were tested in acetonylacetone cyclisation as a probe reaction. A tubular, down-flow reactor was used in experiments carried out at atmospheric pressure, using nitrogen as a carrier gas. The catalyst bed (0.05 g) was first activated for 2 h at 723 K under nitrogen flow (40 cm^3 min^{-1}). Afterwards, a



Scheme 2. Acetonylacetone cyclisation.



Scheme 3. Preparation of 4-aryl-1,4-dihydropyridines (3) from reaction of alkyl bencilidenacetoacetate (1) with β-aminocrotonate (2).

$0.5\ cm^3\ min^{-1}$ of acetonylacetone (Fluka, GC grade) was passed continuously over the catalyst at 623 K. The substrate was delivered with a pump system and vaporized before it was passed through the catalyst bed in the presence of a flow of nitrogen carrier gas ($40\ cm^3\ min^{-1}$). Reaction products were collected during 30 min downstream of the reactor in the cold trap (solid CO_2) and analysed by gas chromatography (GC 8000 Top equipped with a capillary column of DB-1, operated at 353 K, attached to a FID).

2.3. Knoevenagel condensation

The prepared catalysts were tested in liquid phase Knovenagel condensation of benzaldehyde with ethyl cyanoacetate ($pK_a = 9$), ethyl acetoacetate ($pK_a = 10.7$) and diethyl malonate ($pK_a = 13.3$). An equimolecular solution of the two reactants, without any solvent, was kept in a batch reactor in a silicone bath under magnetic stirring, while heating up to the reaction temperature (413–423 K). Then, depending on the active methylenic compound employed, 1, 2 or 10% of catalyst was added and the reaction time started. Samples were taken periodically, and the evolution of the reaction was followed by GC–MS.

The preparation of 1,4-dihydropyridine intermediates of type ethyl benziliden acetoacetate, was carried out using an equimolar solution (7 mmol) of the two reactants (substituted benzaldehydes and ethyl acetoacetate) without any solvent. The mixture was kept in a Pyrex-glass batch reactor in a silicone bath under magnetic stirring, while heating up to the reaction temperature (413 K). Then, 2 wt.% of catalyst was added and the reaction time started. Samples were taken periodically and the evolution of the reaction between 1 and 4 h was followed by GC–MS.

3. Results and discussion

The data calculated from the nitrogen adsorption at 77 K are shown in Table 1. In general, the BET surface area of mesoporous niobosilicate NbMCM-41 and silicate MCM-41 decreases after the impregnation with alkali metal acetate followed by the calcination. This is accompanied by a decrease of single point pore volume. That effect is much higher for alkali metal modified MCM-41 than for NbMCM-41-based samples. Because of the isomorphous substitution of siliceous with niobium in NbMCM-41 the pore size is much higher than in the silicate MCM-41 and it causes the lower blocking effect after alkali metal impregnation.

XRD patterns as well as nitrogen adsorption isotherms (not shown here) confirmed the hexagonal arrangement of mesopores in all alkali metal modified samples. However, they reveal a partial disordering of that arrangement. This effect increases from lithium to cesium impregnated sample and it is less pronounced when NbMCM-41 support is applied. It indicates that niobium in MCM-41 matrix plays a role of structural promoter which prevents the disordering of the materials.

Table 1
Textural parameters of the catalysts.

Catalyst	S_{BET} ($m^2\ g^{-1}$)	V_t ($cm^3\ g^{-1}$)	w_{KJS} (nm)
NbMCM-41	976	1.10	6.6
Li/NbMCM-41	844	0.80	7.3
Na/NbMCM-41	817	0.78	9.1
K/NbMCM-41	623	0.63	10.6
Rb/NbMCM-41	631	0.61	8.2
Cs/NbMCM-41	530	0.56	11.1
MCM-41	1107	1.27	5.8
Li/MCM-41	762	0.72	6.3
Na/MCM-41	746	0.77	6.5
K/MCM-41	462	0.52	7.5
Rb/MCM-41	365	0.44	8.6
Cs/MCM-41	450	0.49	8.6

S_{BET}—BET specific surface area, V_t—single point pore volume, and w_{KJS} —pore width calculated by the BJH–KJS method.

The presence of Nb in mesoporous structure (documented in Refs. [16–18]) not only increases the stability of the solid in the alkali medium but also influences the activity and selectivity of the alkali modified samples in the basic catalysed reactions. Two types of such reactions have been applied in this work, acetonylacetone cyclisation and Knoevenagel condensation. It is known [19,20] that in acetonylacetone cyclisation dimethylfuran (DMF) is produced on Brønsted acid centres, whereas Brønsted basic centres are involved in the formation of methylcyclopentenone (MCP). The activity of all the samples studied was in the range between 20% and 30% of acetonylacetone conversion. The pristine supports activate the reaction towards DMF, whereas the presence of alkali modifiers totally changes the selectivity (Fig. 1). Interestingly, when silicate MCM-41 is used the selectivity in this reaction is irrespective of the nature of alkali metal. Contrary, the application of NbMCM-41 support causes the volcanic dependence of MCP selectivity from the nature of alkali metal element. It is caused by the chemical interaction between niobium species in the support and alkali metal species loaded. Such interaction, different for various alkali metal elements, causes changes in the strength of chemisorption of reagents and their further transformation.

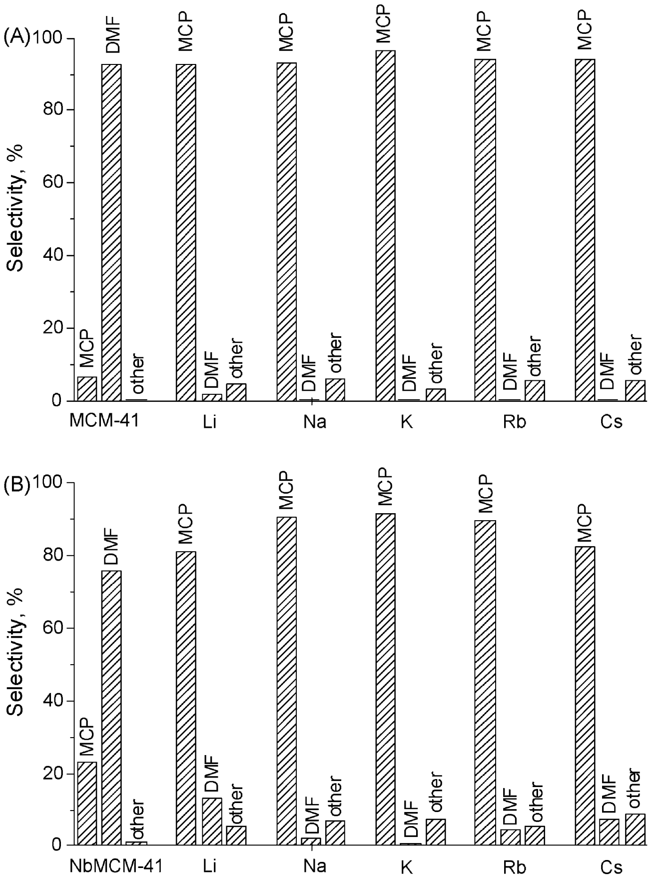


Fig. 1. Selectivity in acetonylacetone cyclisation at 623 K on alkali modified MCM-41 (A) and NbMCM-41 (B) catalysts (other = bi-c-hexanon, hexadienol).

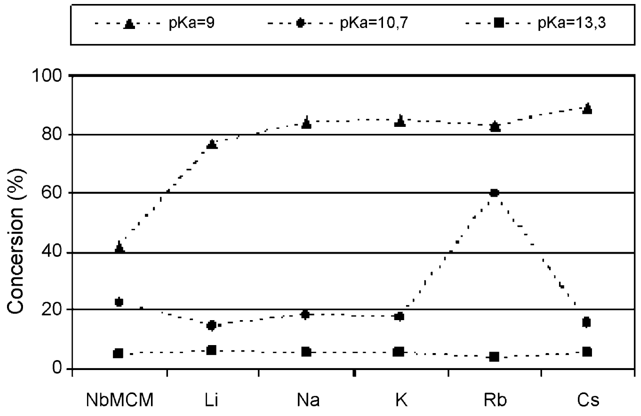


Fig. 2. Condensation of benzaldehyde and ethyl cianoacetate ($pK_a = 9$), ethyl acetoacetate ($pK_a = 10.7$) at 413 K and diethyl malonate ($pK_a = 13.3$) at 423 K. Time reaction: 60 min.

The condensation between benzaldehyde and the three active methylenic compounds (ethyl cyanoacetate, $pK_a = 9$; ethyl acetoacetate, $pK_a = 10.7$ and diethyl malonate, $pK_a = 13.3$) was carried on all the samples listed in Table 1 (particle size within 0.074 and 0.140 mm) at 413 and 423 K, respectively.

The values obtained for the conversion of benzaldehyde in the Knoevenagel condensation with the three active methylenic compounds after 1 h of the reaction are shown in Fig. 2. The selectivity to the Knoevenagel product is 100% for the reactions at $pK_a = 9$ and 13.3, whereas in the reaction performed at $pK_a = 10.7$ secondary products are also formed. Thus, 1 mol of the Knoevenagel product could condense again with another mole of ethyl acetoacetate to give different products and also the ethyl acetoacetate could suffer self-condensation. The activity increases with time of the reaction and the sequence of activity depending on the nature of alkali element varies at various reaction time. It can be illustrated by the reaction curves plotted vs. time of the process. The example is given for the Knoevenagel condensation of benzaldehyde and ethyl acetoacetate (Fig. 3). Interestingly, similar like in the case of acetonylacetone cyclisation, the difference in the activity of various alkali metals modifying mesoporous supports is much higher when NbMCM-41 is used as the matrix for alkali metals. Again the statement concerning the chemical interaction between niobium and alkali metal species is confirmed by this phenomenon. The high conversion in this reaction is reached very fast on Rb/NbMCM-41. Moreover, it is the only catalyst that gives rise to 100% Knoevenagel product selectivity after 4 h of the reaction between benzaldehyde and ethyl acetoacetate ($pK_a = 10.7$). Therefore, this catalyst was chosen to the further study of the condensation of benzaldehyde and substituted benzaldehydes (2-nitrobenzaldehyde and 4-nitrobenzaldehyde) with ethyl acetoacetate (2) (Scheme 1) towards the preparation of 1,4-dihydropyridine intermediates of the type (1) (Scheme 1).

The reactions were carried out at 413 K. The results obtained for the condensation of ethyl acetoacetate with benzaldehyde derivatives are shown in Fig. 4. The yields overcame 50% in the case of the unsubstituted benzaldehyde after 2 h of the reaction and reach 30% in the case of the substituted benzaldehydes due to the major steric impediment. From 120 min of reaction no significant changes were observed in the yield of the reaction due to the poisoning of the active sites of the catalyst by the presence of secondary products from oxidation of benzaldehyde to benzoic acid, ethyl acetoacetate self-condensation and condensation of the Knoevenagel product with another molecule of ethyl acetoacetate.

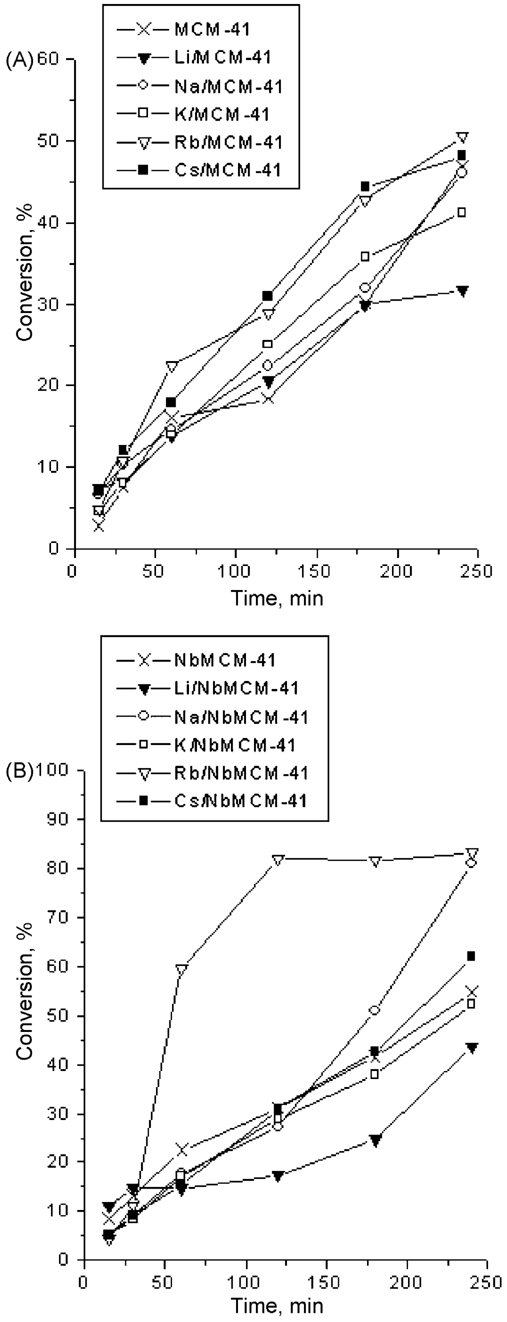


Fig. 3. Conversion in the Knoevenagel condensation ($pK_a = 10.7$). Catalysts based on MCM-41 (A) and NbMCM-41 (B).

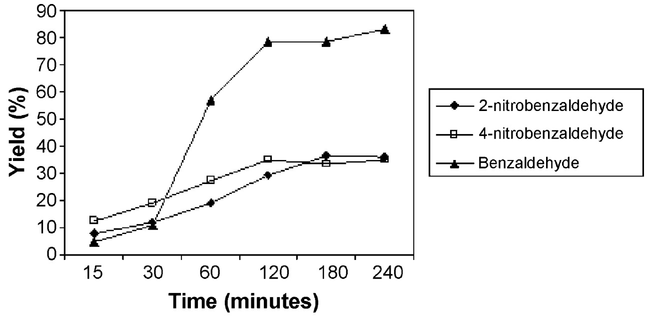


Fig. 4. Condensation of benzaldehyde ($R_1 = H$, $R_2 = H$) 2-nitro ($R_1 = NO_2$, $R_2 = H$) and 4-nitro-benzaldehyde ($R_1 = H$, $R_2 = NO_2$) with ethyl acetoacetate at 413 K using Rb/NbMCM-41 as catalyst.

4. Conclusions

Niobium located in the mesoporous material of MCM-41 type plays a role of structural promoter which prevents the solid from the disordering caused by the treatment with alkali metal solution. Moreover, it changes the catalytic properties of basic centres generated by alkali metal loading in relation to those observed for alkali metals supported on silicate MCM-41. Alkali metal modified NbMCM-41 materials appeared to be attractive catalysts for the acetonylacetone cyclisation and Knoevenagel condensation. Especially, 100% selectivity to Knoevenagel product obtained on Rb/NbMCM-41 in the reaction between benzaldehyde and ethyl acetoacetate ($pK_a = 10.7$) made this catalyst interesting for the further study.

In this work, we present a clean and green method to prepare intermediate compounds for the synthesis of some 1,4-dihydropyridines in liquid phase using alkali modified mesoporous niobosilicate as catalysts in the absence of any solvent. Thus, we report Rb/NbMCM-41 catalyst as a model of an active and selective catalyst in this synthesis by condensation of benzaldehyde and different substituted benzaldehydes with ethyl acetoacetate.

Acknowledgements

Z.Z. thanks Socrates Program of UE for the possibility to stay at Universidad Nacional de Educación a Distancia (UNED) (Madrid, Spain) and V.C.C. also thanks UNED for a Ph.D. fellowship.

References

[1] R.A. Sheldon, I. Arends, U. Hanefeld, Green Chemistry and Catalysis, Wiley–VCH, 2007.
[2] M. Poliakoff, P. Licence, Nature 450 (2007) 810.
[3] J. de D. López-González, A.J. López Peinado, R.M. Martín-Aranda, M.L. Rojas-Cervantes, Carbon 31 (1993) 1231.
(4(E. Perozo-Rondón, V. Calvino-Casilda, R.M. Martín-Aranda, B. Casal-Piga, C.J. Durán-Valle, M.L. Rojas-Cervantes, Appl. Surf. Sci. 252 (2006) 6080.
[5] D.J. Triggle, Cell Mol. Neurobiol. 23 (2003) 293.
[6] S. Mahmoud, A. Ali, E. Hosny, F. Hassan, Bioorg. Med. Chem. 11 (2003) 1865.
[7] F. Bossert, H. Meyer, E. Wehinger, Angew. Chem. Int. Ed. Engl. 20 (1981) 762.
[8] A. Michalska, M. Daturi, J. Saussey, I. Nowak, M. Ziolek, Micropor. Mesopor. Mater. 90 (2006) 362.
[9] J.S. Beck, J.C. Vartuli, W.J. Roth, M.E. Leonowicz, D.T. Kresge, K.D. Schmitt, C.T.W. Chu, D.H. Olson, E.W. Sheppard, S.B. McCullen, J.B. Higgins, J.L. Schlenker, J. Am. Chem. Soc. 114 (1992) 10834.
[10] M. Ziolek, I. Nowak, Zeolites 18 (1997) 356.
[11] M. Kruk, M. Jaroniec, Chem. Mater. 13 (2001) 3169.
[12] E.P. Barrett, L.G. Joyner, P.P. Halenda, J. Am. Chem. Soc. 73 (1951) 373.
[13] M. Kruk, M. Jaroniec, A. Sayari, Langmuir 13 (1997) 6267.
[14] M. Kruk, M. Jaroniec, J. Phys. Chem. B 106 (2002) 4732.
[15] M. Jaroniec, M. Kruk, A. Sayari, in: L. Bonneviot, F. Beland, C. Danumah, S. Kaliaguine (Eds.), Mesopor. Mol. Sieves 117 (1998) 325.
[16] M. Ziolek, I. Sobczak, I. Nowak, P. Decyk, A. Lewandowska, J. Kujawa, Micropor. Mesopor. Mater. 35–36 (2000) 195.
[17] M. Ziolek, I. Sobczak, A. Lewandowska, I. Nowak, P. Decyk, M. Renn, B. Jankowska, Catal. Today 70 (2001) 169.
[18] M. Ziolek, Catal. Today 78 (2003) 47.
[19] R.M. Dessau, Zeolites 10 (1990) 205.
[20] J.J. Alcaraz, B.J. Arena, R.D. Gillespie, J.S. Holmgren, Catal. Today 43 (1998) 89.