Catalysis Communications 11 (2010) 679–683

Contents lists available at ScienceDirect

Catalysis Communications

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

Knoevenagel condensation catalyzed by chemo-selective Ni-nanoparticles in neutral medium

Ajeet Kumar [a], Manika Dewan [a], Amit Saxena [a], Arnab De [b,1], Subho Mozumdar [a,*]

[a] Department of Chemistry, University of Delhi, Delhi-7, India
[b] Indiana University, Bloomington, USA

ARTICLE INFO

Article history:
Received 12 November 2009
Received in revised form 20 January 2010
Accepted 25 January 2010
Available online 1 February 2010

Keywords:
Knoevenagel condensation
Ni-nanoparticles
Neutral medium
Active methylene compounds

ABSTRACT

Recyclable Ni-nanoparticles provides an efficient, economic and rapid method for catalyzing Knoevenagel condensation of aldehydes with an active methylene compound at room temperature. The method offers high yield preferably in case of aromatic aldehydes and proceed well in neutral medium. This method provides a wide range of substrate applicability and simple workup procedure. The products need no further purification and the process is environmentally benign.

1. Introduction

The Knoevenagel condensation is a useful carbon–carbon bond forming reaction [1,2] with numerous applications in the synthesis of fine chemicals [3], hetero-Diels–Alder reactions [4] and in the synthesis of carbocyclic as well as hetero cyclic [5] compounds. The reaction has been utilized in the preparation of coumarin derivatives [6], cosmetics [7], perfumes [8] and pharmaceutical chemicals [9]. Traditionally, this condensation has been carried out between a carbonyl compound and an active methylene compound in the presence of bases such as ethylenediamine [10], piperidine [11] or corresponding ammonium salts [12], amino acids [13], dimethylaminopyridine [14] and potassium fluoride mixture [15]. Recently, many efforts have been made to prepare electrophilic alkenes by conducting this reaction under heterogeneous conditions [16] using inorganic salts like Al_2O_3 [17], zeolite [18] and calcite [19]. Ionic liquids [20] have also played a vital role as a reaction media for this condensation. However, some of these processes require harsh conditions and suffer from a lack of generality. Hence, there is an existing need for the development of milder methods for obtaining these products under conditions tolerated by sensitive functional groups from both synthetic and environmental points of view. The synthetic challenge is to carry out this reaction in a neutral medium thus avoiding the use of bases. The role of Ni-nanoparticles in dehydration chemistry has been well documented elsewhere by our research group [21–23]. The process is cost-effective and eco-friendly as it does not require elevated temperatures, harsh bases and is an excellent methodology for carrying out the reaction in a neutral medium. Moreover, it is a one pot synthesis and has an easy work up and product isolation procedure. Finally, the use of Nickel-nanoparticles owing to their recyclability makes the procedure eco-friendly, as in typical cases where metal salts and other complexes are used as catalysts, an excessive amount of catalysts (usually in grams) is needed and this is eliminated as a ‘waste product/contaminant’ generating unwanted toxicity and pollution. The quantity of catalyst that we use here is in microgram scales, thereby reducing the level of toxic waste. It may be additionally noted that in the recent past Ni-nanoparticles have been used for various applications including *in vivo* and *in vitro* treatment of living cells/organisms and no evidence of toxicity has been reported for low dosages [24–26]. Therefore, we can claim that our method is eco-friendly and environmentally benign. Furthermore, recycling/reusability of Ni-nanoparticles can decrease the generation of toxic waste and thereby minimizing contamination. It has been observed that the Nickel-nanoparticles prepared as per our procedure [21–23] could be stored easily in absolute ethanol for long duration (>2 months) retaining their catalytic activity.

2. Results and discussion

In this communication, we wish to highlight our findings on the Ni-nanoparticles catalysed condensation of active methylene compounds, such as malonic acid, ethyl cynoacetate, malononitrile and

---

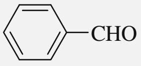
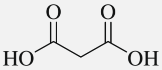
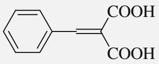
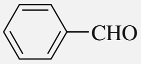
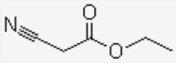
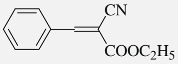
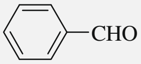
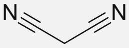
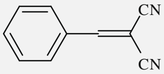
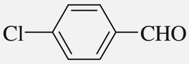
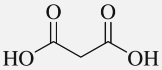
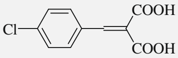
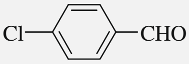
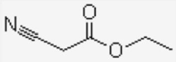
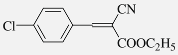
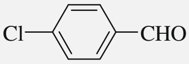
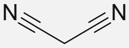
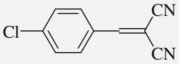
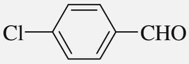
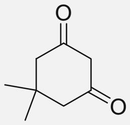
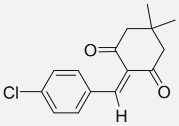
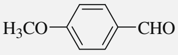
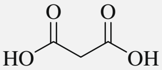
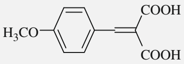
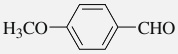
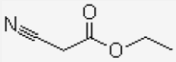
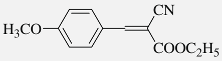
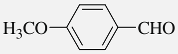
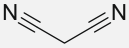
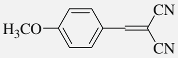
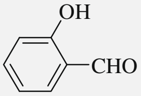
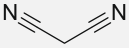
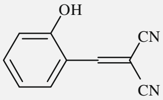
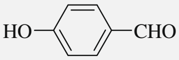
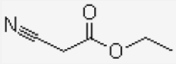
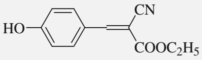
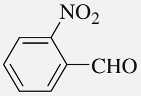
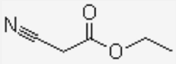
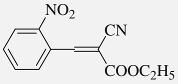
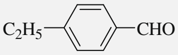
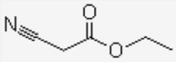
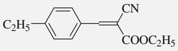
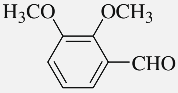
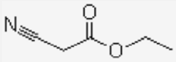
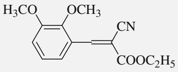
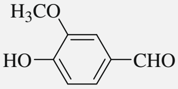
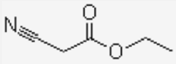
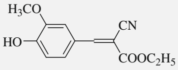
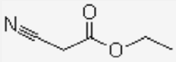
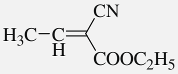
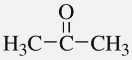
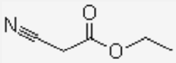
* Corresponding author. Fax: +91 11766 6593.
E-mail address: subhoscom@yahoo.co.in (S. Mozumdar).

[1] Present address.

1566-7367/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.catcom.2010.01.017

Table 1

Ni-nanoparticles catalysed Knoevenagel condensation of aldehydes with active methylene compounds.[a]

Entry	Carbonyl compound	Active methylene compounds	Products	Time (h)	Yield (%) [b,c]
1				0.30	98
2				0.58	97
3				0.33	98
4				0.50	92
5				0.75	95
6				0.25	97
7				1.00	81
8				1.16	92
9				1.41	97
10				0.83	94
11				0.41	85
12				0.75	89
13				0.83	91
14				1.33	72
15				1.25	80
16				0.41	83
17	H_3C-CHO		 $H_3C-\underset{H}{C}=C(CN)COOC_2H_5$	4.16	5
18	 $H_3C-\overset{O}{\overset{\Vert}{C}}-CH_3$		–	12.00	–

[a] Reaction condition: 5 mmol of aldehydes, 6 mmol of active methylene compound, 10 mol% Ni-nanoparticles (15–20 nm); Ethanol; 25 °C 1 atm.

[b] Confirmed by comparison with authentic samples (FT-IR, ^{1}HNMR, ^{13}CNMR, TLC, MP/BP).

[c] Isolated and unoptimised yields.

dimedone with aldehydes at room temperature in a neutral medium. It may be postulated that the nanoparticles play a complex redox role in accelerating the condensation reaction [27] and thus may promote the formation of Knoevenagel products. Moreover, because of their higher surface-to-volume ratio, nanoparticles can provide increased surface area which in turn can enhance the rate of the reaction. In general, substituents at the ortho-position of the aromatic aldehydes (Table 1:11, 13 and 15) seemed to

Table 2
The effect of Ni-nanoparticles concentration on the Knoevenagel condensation at room temperature under air atmosphere (Table 1, Entry 3)[a].

Catalyst concentration (Ni-np) (mol%)	Time (h)	Yield (%)[b,c]	TOF (s^{-1})
No catalyst	24	–	–
2	1	52	7.2×10^{-3}
5	1	85	4.2×10^{-3}
10	1	98	2.7×10^{-3}
20	1	98	1.3×10^{-3}

[a] Reaction condition: 5 mmol of aldehydes, 6 mmol of active methylene compound, Ni-nanoparticles (15–20 nm); Ethanol; 25 °C 1 atm.
[b] Confirmed by comparison with authentic samples (FT-IR, ^{1}HNMR, ^{13} C-NMR, TLC, M.P/B.P).
[c] Isolated and unoptimised yields.

Table 3
Reuse of Ni-nanoparticles for the formation of Knoevenagel products[a].

Run	Table 1, Entry 1		Table 1, Entry 3	
	Time (h)	Yield (%)[b,c]	Time (h)	Yield (%) [b,c]
1	1	96	1	98
2	1	91	1	97
3	1	82	1	89
4	1	78	1	70
5	1	42	1	51

[a] Reaction condition: 5 mmol of aldehydes, 6 mmol of active methylene compound, 10 mol% Ni-nanoparticles (15–20 nm); Ethanol; 25 °C;1 atm.
[b] Confirmed by comparison with authentic samples (FT-IR, ^{1}HNMR, ^{13}CNMR, TLC, M.P/B.P).
[c] Isolated and unoptimised Yields.

decrease the rate of the reaction together with the overall yield and this may be because of steric constraints offered to the incoming nucleophile. Ketones showed no reactivity at all under the same conditions (Table 1:18).

3. Catalyst concentration

Catalyst concentration was found to be another influencing parameter that plays a major role in optimizing the product yield. The yield generally increased with the increasing concentration of the catalyst; however increasing the molar concentration of the Ni-nanoparticles (15–20 nm) from 10 to 20 mol% did not substantially increase the yield of the product (Table 2). Hence, a concentration of 10 mol% of Ni-nanoparticles was considered as a suitable choice for the optimum yield of Knoevenagel products. It has been observed that per mole of catalyst could convert 23.43×10^{15} moles of substrate into products before getting deactivated i.e. a TON value of 23.43×10^{15} could be achieved using Ni-nanoparticles as catalyst.

4. Solvent effects

The solvent used have a strong effect in deciding the reaction path and the nature of the product. Usually, the increase in polarity leads to increase in reaction rate. This behavior is attributed to the influence of the solvent on the transition state and to a change in the capacity of the catalyst for proton transfer:when polar reagents are involved, the transition-state complex is better solvated by polar solvents and the partition of the reactants at the solid–liquid interface is higher, decreasing the activation free enthalpy and enhancing the reaction rate [28,29]. The Knoevenagel condensation between benzaldehyde and malanonitrile was also investigated in various solvents such as CH_3CN, DMF, DMSO, $CHCl_3$ and Ethanol with all the other parameters kept constant and the progress of the reaction was checked through TLC. The yields were found to be 45%, 85%, 98%, 32%, and 98%, respectively. Hence, out of ethanol and DMSO, ethanol was used as solvent through out the reaction course as the removal of DMSO from the reaction mixture is quite difficult.

5. Recyclability of catalyst

Further, the use of Ni-nanoparticles as a recyclable catalyst was tested by carrying out repeated runs of the reaction on the same batch of the catalyst system (Table 3). The data shows a gradual loss of the activity of the catalyst used in the experiment with the increasing number of cycles. It was found from QELS, TEM and XRD data (see supporting information for details) that the Ni-nanoparticles underwent aggregation as well as oxidation (Nickel to Nickel oxide) during the course of reaction and recycling of catalytic Ni-nanoparticles. Hence, it may be proposed that both the factors together were responsible for the decrease in catalytic activity of Ni-nanoparticles.

6. Experimental

6.1. General remarks

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. All reactions were monitored by thin layer chromatography (TLC) on gel F254 plates. The silica gel (250–400 meshes) for column chromatography was purchased from Spectrochem Pvt. Ltd., India. ^{1}HNMR (400 MHz) and ^{13}CNMR spectra were recorded in $CDCl_3$ on a AMX 400 spectrometer (with TMS for ^{1}H and $CDCl_3$ for ^{13}CNMR as internal references); software IRIX 6.5/XWINNMR. MS were recorded on ESI-Mass spectrometer Model-Esquire 3000 Plus (Bruker Daltonics Data analysis 3.1). Melting points were recorded on Buchi melting point 540 instruments. The size and morphology of Ni-nanoparticles were characterized with the help of transmission electron microscope (TEM, FEI Philips Morgani 268D model Acc. voltage:70 kV with magnification:upto 80,000×) and Quasi Elastic Light Scattering instrument (QELS, Photocor-FC, model-1135 P) and the metallic nature of the particles was confirmed with UV-spectrophotometer (Hitachi AU-2700).

6.2. Preparation of nickel-nanoparticles

A chemical method involving reduction of Ni^{2+} ions to Ni (0) in a reverse micellar system was employed to prepare the Nickel-nanoparticles. Triton X-100 (TX-100) was used as the surfactant, cyclohexane as the solvent (continuous phase), hexanol as co-surfactant and aq. solution of salts as dispersed phase. The reverse micelles were prepared by dissolving TX-100 in cyclohexane (usually 0.08–0.15 M of TX-100 solution). A typical preparative method is as follows: to a set volume of 100 ml (0.1 M TX-100 solutions in cyclohexane) 900 μl of $Ni(NO_3)_2$ aq. solution (2% w/v) and hexanol (quantity sufficient, q.s.) was added to prepare an optically clear reverse micellar solution (RM-1). To another 100 ml (0.1 M TX-100 solution in cyclohexane) alk. solution of $NaBH_4$ (5% w/v in 2% NaOH w/v aq. solution) and hexanol (q.s.) was added to obtain RM-2. To the prepared reverse micellar solution of $Ni(NO_3)_2$ aq. solution (2% w/v) (RM-1) another reverse micellar, alk Solution of $NaBH_4$ (5% w/v in 2% NaOH w/v aq. solution) (RM-2) was added drop wise with constant stirring maintaining the nitrogen atmosphere. In the presence of nitrogen atmosphere the resulting solution was kept on further stirring for 3 h to allow complete Ostwald Ripening (particle growth). The Ni-nanoparticles were extracted by adding absolute ethanol to the resulting reverse micellar solution followed by centrifugation at 3000–4000 rpm for 10 min. By varying the water con-

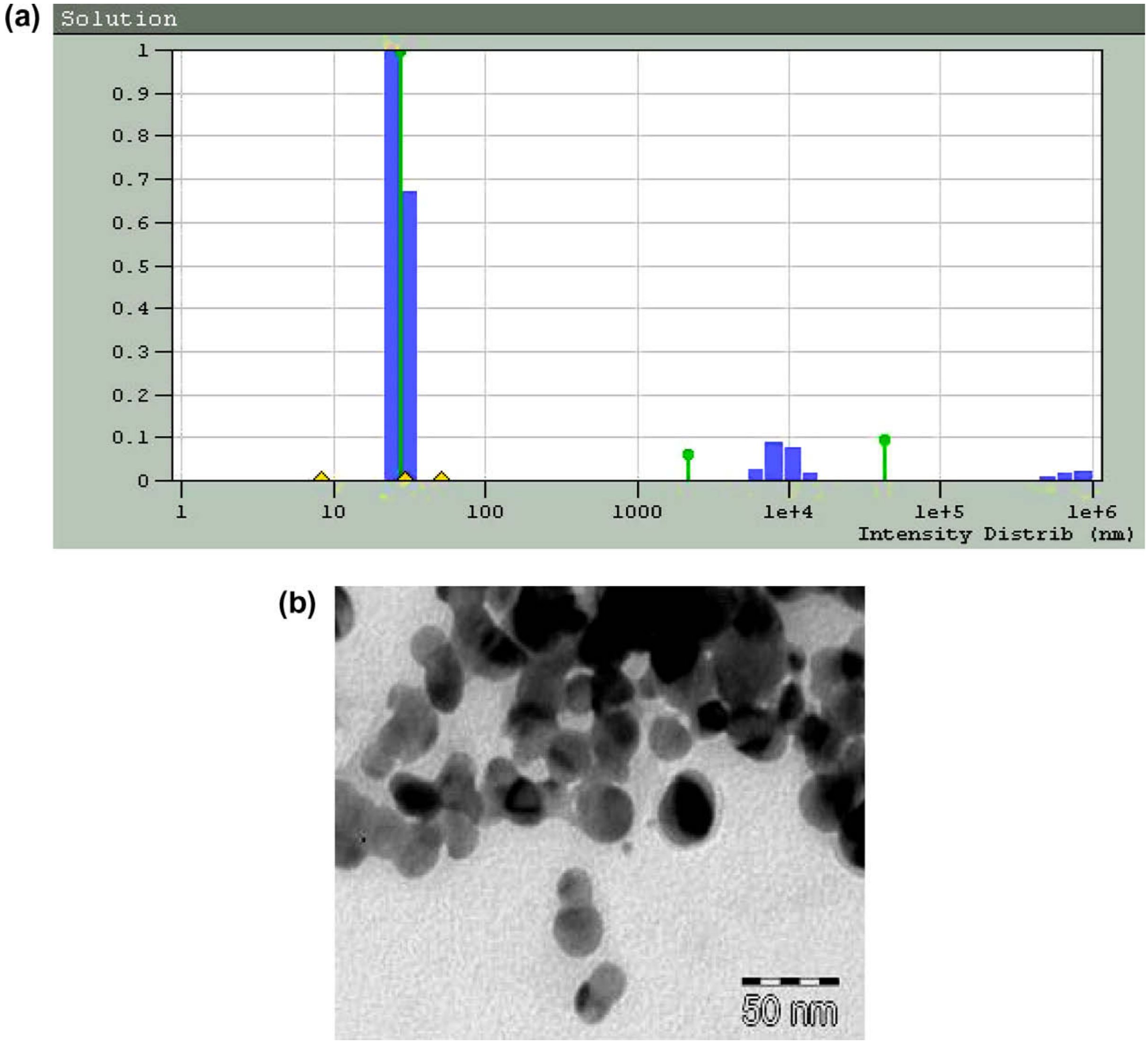


Fig. 1. (a) QELS data of Ni-nanoparticles: plot of population distribution in percentile versus size distribution in nanometre, (b) TEM image of Ni-nanoparticles. The scale bar corresponds to 50 nm in the TEM image.

tent parameter Wo (defined as the molar ratio of water to surfactant concentration, Wo = [H_2O]/[surfactant]) the size of the nanoparticles could be controlled. The sizes of the Ni-nanoparticles prepared at Wo value of 5 were confirmed as 15–20 nm through Quasi Elastic Light Scattering (QELS) (Fig. 1a) and transmission electron microscopy (TEM) technique (Fig. 1b). The Ni-nanoparticles prepared were round in shape and black in color (in colloidal state).

6.3. Typical procedure for the Ni-nanoparticles catalysed Knoevenagel product

To a mixture of aldehydes (5.0 mmol), active methylene compound (6.0 mmol) in Ethanol (10 ml) Ni-nanoparticles were added as catalyst (15–20 nm, 10 mol%). The resulting reaction mixture was stirred at room temperature for a specified period (Table 1). The progress of the reaction was monitored by thin layer chromatography (TLC), after complete conversion, as indicated by TLC; the reaction mixture was diluted by adding Ethyl acetate (50 ml) and washed with water thrice followed by brine. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4) followed by evaporation of solvent using a rotary evaporator under reduced pressure and concentrated to dryness gave the desired product, which after re-crystallisation afforded the pure Knoevenagel products (Table 1). The analysis of complete spectral and compositional data revealed the formation of Knoevenagel products with excellent purity.

6.4. Typical procedure for the recycling of the Ni-nanoparticles (catalyst)

After completion of the reaction (as confirmed by TLC), the reaction mixture was centrifuged at 4000–6000 rpm for 10 min, which precipitated the Ni-nanoparticles as solid pellet at the bottom of the centrifuge tube. The nanoparticles were washed with Ethanol 4–5 times to confirm the complete removal of any residual material. The particles were then redispersed in the Ethanol for further catalytic reaction cycles. The same process was repeated after each reaction cycle to isolate and reuse the Ni-nanoparticles as catalyst.

Acknowledgements

Dr. S. Mozumdar and Ajeet Kumar gratefully acknowledges financial support from the Department Biotechnology, Govt. of INDIA (BT/PR8918/NNT/28/05/2007) and the help of Professor P. Balram, Director, Indian Institute of Science, Bangalore for his help in the Mass and NMR characterization done in this work.

Appendix A. Supplementary data

Experimental procedures as well as the characterization of the Nickel-nanoparticles (TEM, QELS and XRD) and compounds (FT-IR, ^{1}HNMR, ^{13}CNMR and Mass spectra) are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.catcom.2010.01.017.

References

[1] E. Knoevenengel, Chem. Ber. 31 (1898) 2585.
[2] G. Jones, Org. React. 15 (1967) 204.
[3] L.F. Tietze, P. Saling, Synlett (1992) 281.
[4] I. Kim, S.G. Kim, J. Choi, G.H. Lee, Tetrahedron 64 (2008) 664.
[5] L.F. Tietze, Chem. Rev. 96 (1996) 115.
[6] A. Song, X. Wanga, K.S. Lam, Tetrahedron Lett. 44 (2003) 1755.
[7] N. Yu, J.M. Aramini, M.W. Germann, Z. Huang, Tetrahedron Lett. 41 (2000) 6993.
[8] S. Balalaie, A.M. Sheikh, M. Bararjanian, Catal. Commun. 8 (2007) 1724.
[9] F. Bigi, L. Chesini, R. Maggi, G.J. Sartori, Org. Chem. 64 (1999) 1033.
[10] L.F. Tietze, J. Wölfling, G. Schnider, Chem. Ber. 124 (1991) 591.
[11] C. Xing, S. Zhu, J. Org. Chem. 69 (2004) 6486.
[12] E.J. Cragoe Jr, C.M. Robb, J.M. Spragne, J. Org. Chem. 15 (1950) 381.
[13] G. Cardilla, S. Fabbroni, G. Luca, G. Massimo, A. Tolomelli, Synth. Commun. 9 (2003) 1587.
[14] A.V. Narsaiah, A.K. Basak, B. Visali, K. Nagaiah, Synth. Commun. 34 (2004) 2893.
[15] S. Sebti, A. Smahi, A. Solhy, Tetrahedron Lett. 43 (2002) 1813.
[16] V.S.R. Rajasekhar Pullabhotla, A. Rahman, S.B. Jonnalagadda, Catal. Commun. 10 (2009) 365.
[17] J.A. Cabello, J.M. Campelo, A. Garcia, D. Luna, J.M.J. Marinas, Org. Chem. 49 (1984) 5195.
[18] T.I. Reddy, R.S. Varma, Tetrahedron Lett. 38 (1997) 1721.
[19] S. Wada, H. Suzuki, Tetrahedron Lett. 44 (2003) 399.
[20] J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, Tetrahedron Lett. 44 (2003) 1047.
[21] A. Saxena, A. Kumar, S. Mozumdar, Appl. Catal. A 317 (2007) 210.
[22] A. Kumar, S. Kumar, A. Saxena, S. Mozumdar De, Catal. Commun. 9 (2008) 778.
[23] A. Kumar, S. Kumar, A. Saxena, A. De, S. Mozumdar, Catal. Lett. 122 (2008) 98.
[24] J. Dobson, Gene Ther. 13 (2006) 283.
[25] R. Zhang, X. Wang, C. Wu, M. Song, J. Li, G. Lv, J. Zhou, C. Chen, Y.D.F. Gao, D. Fu, X. Li, Z. Guan, B. Chen, Nanotechnol. 17 (2006) 3622.
[26] D.D. Guo, C.H. Wu, X.M. Wang, B.A. Chen, Chin. Chem. Lett. 19 (2008) 577.
[27] W. Yan, R. Wang, Z. Xua, J. Xua, L. Lin, Z. Shen, Y. Zhoua, J. Mol. Catal. A: Chem. 255 (2006) 81.
[28] J. Gascon, U. Aktay, M.D. Hernandez-Alonso, G.P.M. Van Klink, F. Kapteijn, J. Catal. 261 (2009) 75.
[29] A. Corma, S. Iborra, I. Rodríguez, F. Sánchez, J. Catal. 211 (2002) 208.