

## POLYETHYLENEIMINE (PEI) ON SILICA AS CATALYST IN KNOEVENAGEL AND MICHAEL REACTIONS

Fatiha Zaoui<sup>1,2\*</sup>, Didier Villemin<sup>3</sup>, Nathalie Bar<sup>3</sup>, Mohamed A. Didi<sup>2\*</sup>

<sup>1</sup>University of Saïda, Faculty of Sciences, Department of Chemistry,  
PB 139, 20000, Saïda, Algeria

<sup>2</sup>University of Tlemcen, Faculty of Sciences, Department of Chemistry,  
Laboratory of Separation and Purification Technology, PB 119, 13000,  
Tlemcen, Algeria

<sup>3</sup>University of Caen, ENSICAEN, Laboratory of Molecular and  
Thio-organic Chemistry (LCMT), UMR CNRS 6507, INC3M, FR 3038,  
Labex EMC3, 14050 Caen, France

\*Corresponding authors: [zaouifatiha@yahoo.fr](mailto:zaouifatiha@yahoo.fr), [madidi13@yahoo.fr](mailto:madidi13@yahoo.fr)

Received: April, 04, 2016  
Accepted: January, 27, 2017

**Abstract:** After the synthesis of polyethylenimine supported on silica, it has been used as a new and efficient catalyst in Knoevenagel and Michael condensations. The presence of the polyethylenimine in the catalytic system together with silica displays an acido-basic character allows a better catalytic activity in the condensations. Carried out under microwave irradiation, without organic solvent and during short time, the syntheses are respectful towards green chemistry. The solid catalyst can be easily reused. This catalyst has the acido-basic character at the same time.



**Keywords:** catalyst, Knoevenagel, Michael, polyethylenimine, silica

## INTRODUCTION

The use of solid bases was established as a main subject in catalysis. During these last years, the preparation of organic compounds by means of the organic or inorganic heterogeneous catalysts or supported catalysts without using any organic solvent has been a big challenge.

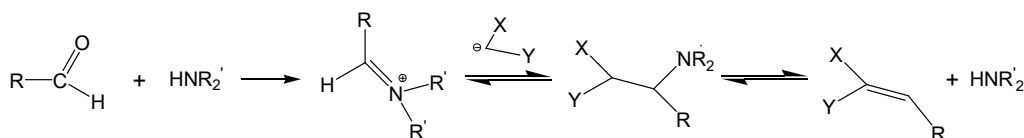
Many inorganic solids with amine functionalities on their surface such as silica [1], alumino-silica [2] and metallo-silica [3] are known. The amino groups were generally introduced *via* the formation of Si-O covalent bond, using commercially available aminopropylsilane. These solids such as SAB [2], MCM-41 [1] and zeolites were used as basic catalyst in Knoevenagel and Michael reactions [4]. Polyethyleneimines (PEI) are commercially available hyperbranched polymers with high level of primary [5], secondary and tertiary amino groups. Polar hydrophilic polymers PEI are very basic. They have been previously used as polymer support for conception of new artificial enzymes (Symzym) by Breslow [6].

For that purpose, we were interested by the application of the silica gel as support for the polyethyleneimine in the synthesis of biomolecules *via* Knoevenagel and Michael reactions. The Knoevenagel reaction lends itself particularly well to microwave activation [7]. It is an equilibrium reaction where a water molecule is released [8]:



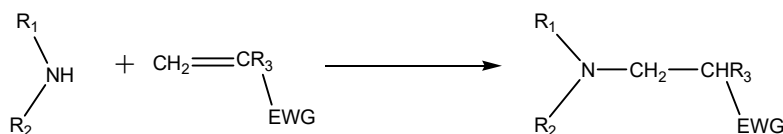
The formed water absorbs strongly the microwaves and is almost evaporated immediately, moving the equilibrium reaction towards the right. The efficiency of the method is also connected to the used reagents. Aldehydes are polar molecules which heat very quickly under microwaves irradiation.

Knoevenagel showed that there was reaction between the aldehyde and amine to give the imine or the iminium salt corresponding, which reacts with the anion derived of the compound with active methylene (Scheme 1):



**Scheme 1.** Knoevenagel condensation catalyzed by primary or secondary amine

Michael's reaction is a mainly nucleophile addition of a amine to an  $\alpha,\beta$ -unsaturated carbonyl compound (aldehyde, ketone,  $\alpha$ -acyloxy nitrile,  $\alpha$ -cyano amide). A variety of amines reacts with  $\alpha,\beta$ -ethylenic compounds to give the products  $\alpha$ -amino correspondents (Scheme 2):



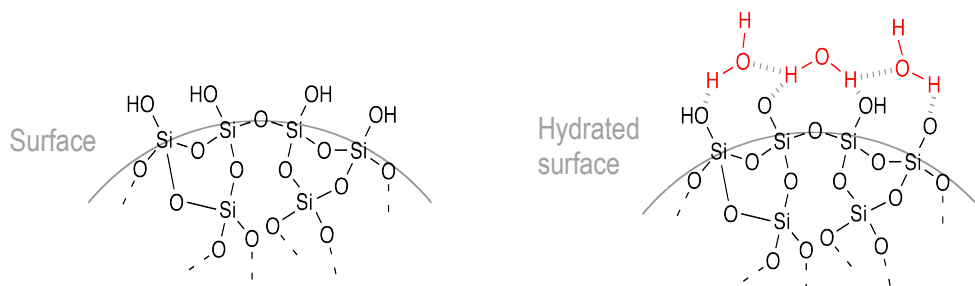
**Scheme 2.** Michael reaction with amines

## EXPERIMENTAL

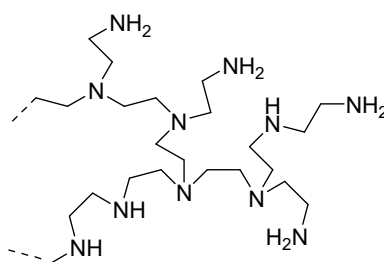
The infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrometer equipped with accessories ATR, from LCMT Caen, France. Samples were analyzed using NMR spectroscopy by a multinuclear Bruker Avance III400-spectrometer, from LCMT Caen, France. Samples of the products were diluted in  $d_6$ -DMSO. Microwave irradiation reactions were performed in a mono-mode resonance microwave oven (Synthewave 402, Prolabo, France) working with the frequency of 2450 MHz, controlled with an IR thermometer and monitoring by a computer, from LCMT Caen. Microanalyses were performed on the automatic C,H,N analyzer ThermoQuest Elemental Analyzer (Model no. 2500, Thermo Quest CE Instruments, France).

### Preparation of Silica/PEI (5/1)

We have prepared a new catalyst PEI supported on silica (PEI-silica), by impregnation of chromatographic silica (20 g) (Silica gel Merck, Grade 7734; 70-230 mesh, (63-200  $\mu\text{m}$ ) and a very large specific area  $500\text{-}600\text{ m}^2\cdot\text{g}^{-1}$ ) (Figure 1), with PEI (MW = 2000 kDa, Lupasol SK 24 % in water) (for instance 1.0 g of PEI in 40 mL ethanol) (Figure 2) (Silica/PEI = 5/1). After stirring, the mixture was evaporated under vacuum, which leads to a white powder not gluing, which was used directly as catalyst.



**Figure 1.** Surface of the dry and hydrated silica gel



**Figure 2.** Structure of PEI

### Irradiation at 800 W

In a typical experiment, a mixture of acidic carbon compound (5 mmol) and aldehyde (5 mmol) was adsorbed on 3 g of catalyst and then the mixture was irradiated at 800 W for different times according to the reactants (3-20 min). The reaction was monitored by taking a small sample of solid, extracting with acetonitrile (1 mL) and analyzing the extract by TLC. When the reaction was completed, the irradiation was stopped and the

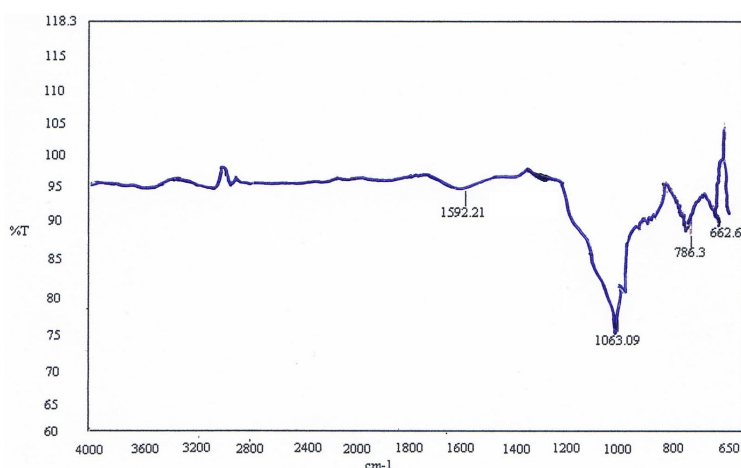
product was extracted by simple elution with dichloromethane or acetonitrile. The solvent was evaporated in vacuum, and the solid obtained was recrystallized or purified by flash chromatography on silica.

$^1\text{H}$  and  $^{13}\text{C}$  NMR, IR spectra, melting point (Mp) and  $R_f$  by TLC were compared with authentic sample.

The reusability of PEI-SiO<sub>2</sub> has been investigated up to five repeated cycles using the synthesis of 1-methoxy-4-(vinylbenzene cyanoethylacetate).

## RESULTS AND DISCUSSION

The catalyst, PEI-SiO<sub>2</sub>, was washed with ( $4 \times 10$  mL) by the acetone and ether, and then dried. The reusability of PEI-SiO<sub>2</sub> has been investigated up to five repeated cycles using the Knoevenagel reaction of methoxybenzaldehyde with ethyl cyanoacetate in the same conditions. No noticeable changes were observed even after five cycles: the stability of catalyst was perfect and indicate that none of reactants/products remain with PEI-SiO<sub>2</sub>. The catalyst, PEI-SiO<sub>2</sub>, was washed with acetonitrile after every cycle and the solid was characterized by FT-IR: 1592.2 cm<sup>-1</sup> (N-H), 1063.1 cm<sup>-1</sup>, 786.3 cm<sup>-1</sup> and 662.6 cm<sup>-1</sup> (Si-O-Si) (Figure 3).



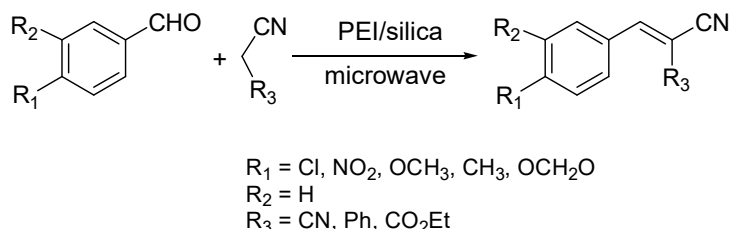
**Figure 3.** FT-IR of PEI-SiO<sub>2</sub>

No noticeable changes were observed even after five cycles (Table 1). The yield of product after separation and isolation in each case was calculated and reported in Table 1. The variation in the yield was found to be in range of 90 - 94 % after optimization of catalyst amount and time. This result indicates the stability of the catalyst and also that none of reactants or products remain on the solid.

**Table 1.** Results obtained using recycled catalyst

Reaction	Cycle	Yield [%]
1	1	94
2	2	94
3	3	91
4	4	90
5	5	90

Knoevenagel reactions (Scheme 3) are catalyzed by basic, acid and acido-basic catalysts [9]. Silica without PEI is often able to catalyze the reaction in solventless conditions with some acidic carbon compounds. We have performed here the reactions without solvent and under microwave irradiation according to the methodology that we have described many years ago [10]. The obtained products present among other effects such as antibacterial activities [11 – 24].



**Scheme 3.** Knoevenagel reaction

Our results (Table 2) show, on the one hand, that the cyano compounds reacts more quickly (8 min) with aromatic aldehydes; on the other hand, the ethyl cyanoacetate requires longer time (15 min). This difference of reactivity is due to CN which has a capacity of electron attraction stronger than the carbonyl or carboxylic groups.

**Table 2.** Knoevenagel reactions under microwave catalyzed by PEI-SiO<sub>2</sub>

Aldehyde, R <sub>1</sub> =	Acidic compound, R <sub>3</sub> =	Time [min]	Yield [%]	Mp [°C] (solvent*)	Lit. Mp [°C] (solvent*)	Ref.
4-nitro	COOEt	15	81	168 (MeCN)	169-170	[1]
4-chloro	COOEt	15	75	92 (EtOH)	89-90 (EtOH)	[2]
4-methyl	COOEt	15	73	92 (EtOH)	92 (EtOH)	[2]
4-methoxy	COOEt	15	78	78 (EtOH)	81-82 (EtOH)	[3]
3,4-methylenedioxy	COOEt	15	70	104 (EtOH)	106-107 (EtOH)	[4]
4-nitro	Ph	20	55	123 (EtOH)	122 (EtOH)	[5]
4-chloro	Ph	20	42	103 (EtOH)	101-101.5 (EtOH)	[5]
4-methyl	Ph	20	40	60 (EtOH)	57.5-59 (EtOH)	[9]
4-methoxy	Ph	20	35	92 (EtOH)	93-94.5 (EtOH)	[9]
3,4-methylenedioxy	Ph	20	38	121(EtOH)	122 (MeOH)	[10]
4-nitro	CN	8	42	163 (MeCN)	158-161	[11]
4-chloro	CN	8	47	129 (MeCN)	128-130	[2]
4-methyl	CN	8	56	160 (MeCN)	158-161(EtOH)	[25]
4-methoxy	CN	8	71	110 (MeCN)	116-117 (EtOH)	[2]
3,4-methylenedioxy	CN	8	65	198 (MeCN)	197-200	[25]

\* Recrystallization solvent

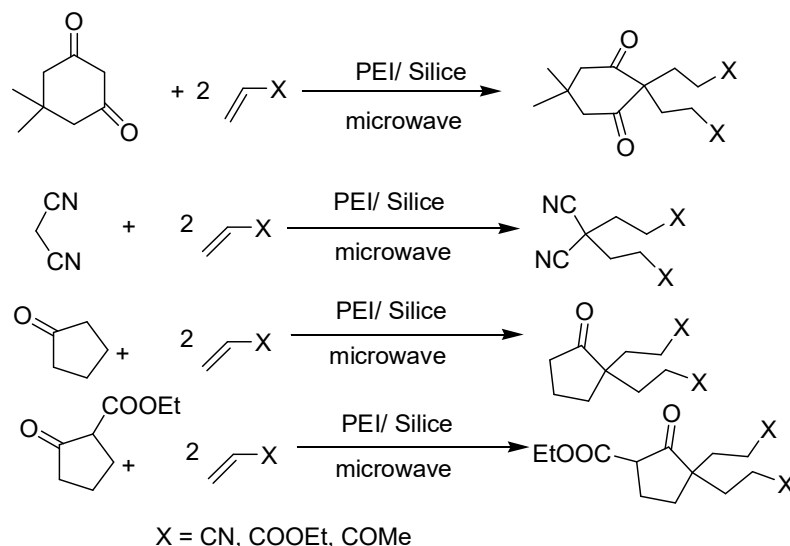
Our results are in agreement with those of Gawande and Jayaram [24], Kaupp *et al.* [26] and Moussaoui and Ben Salem [27].

The reusability of PEI-SiO<sub>2</sub> has been investigated up to five repeated cycles using the Knoevenagel reaction of methoxybenzaldehyde with ethyl cyanoacetate in the same conditions (under microwaves 350 W, 15 min).

The catalyst, PEI-SiO<sub>2</sub>, was washed with acetonitrile after every cycle and the solid was characterized by FT-IR. No noticeable changes were observed even five cycles

(Table 1). This result indicates the stability of catalyst but also none of reactant or products remain on the solid.

We also used the catalytic PEI system / silica to make Michael's addition (Scheme 4) [28]. The dimedone and malononitrile as donor of Michael and the acrylate of ethyl, methyl vinyl ketone and the acrylonitrile as acceptor of Michael, were used.



**Scheme 4.** Michael reaction under microwave irradiations

For this purpose, we have prepared  $\gamma$ -aminopropylsilica as Macquarrie methodology [17], and we have compared this catalyst with the PEI/silica (Table 3). The activity of  $\gamma$ -aminopropylsilica was lower than PEI-silica.

**Table 3.** Michael reactions catalyzed by PEI-SiO<sub>2</sub> under microwave irradiation

Vinyl X=	Acidic carbon compounds	Time (min)	Yield [%]	Mp [°C]	Lit. Mp [°C] (solvent*)	Ref
COOEt	Dimedone	30	35	79	80-81 (EtOH)	[29]
COOEt	Malononitrile	21	34	54		[This work]
CN	Dimedone	8	34	144	139-140	[30]
CN	Malononitrile	8	59	61		[This work]
COMe	Dimedone	20	73	104	101-108 (EtOH)	[31]
COMe	Malononitrile	15	48	84		[This work]
COMe	Cyclopentanone	15	36	83	72-80 at 0.4 Torr	[32]
COMe	Ethyl 2-oxocyclopentane carboxylate	10	41	133	135 at 11 Torr	[33]

Conditions: 2 eq. vinyl X=1 eq. acidic (dimedone or malononitrile).

\*recrystallization solvent

For the Michael reaction, in the presence of polar solvent like methanol, we have observed deactivation for both catalysts. In the case of PEI-silica some desorption of PEI from silica have occurred and with grafted aminopropylsilica [34] cleavage of aminopropylsilyl groups has taken place.

Pure PEI was a less active catalyst than PEI on silica. We attributed the synergic effect of silica to the acidic character of silanol groups on silica.

## CONCLUSIONS

The main advantage of the new catalyst lies on its ease of preparation from commercially available reagents. In presence of a low polar organic solvent, the reuse of catalyst can be of convenient use.

The catalyst PEI/Silica constitutes a basic catalytic means for the Knoevenagel reaction under microwave. The recycling of the catalyst was done easily through a simple wash.

Our catalytic system presents several interests such as efficiency in organic synthesis, simplicity of implementation and recycling of the catalyst.

## REFERENCES

1. Katkar, S.S., Lande, M.K., Arbad, B.R., Rathod, S.B.: Indium modified mesoporous zeolite AlMCM-41 as a heterogeneous catalyst for the Knoevenagel condensation reaction, *Bulletin of the Korean Chemical Society*, **2010**, 31 (5), 1301-1305;
2. Zabicky, J.: The kinetics and mechanism of carbonyl–methylene condensation reactions. Part XI. Stereochemistry of the products, *Journal of the Chemical Society*, **1961**, 683-687;
3. Lee, J., Gauthier, D., Rivero, R.A.: Solid-phase synthesis of 3,4,5-substituted 1,5-benzodiazepin-2-ones, *Journal of Organic Chemistry*, **1999**, 64 (9), 3060-3065;
4. Popp, F.: Notes-Synthesis of 3-hydroxypyridines. I. Condensation of aromatic aldehydes with ethyl cyanoacetate, *Journal of Organic Chemistry*, **1960**, 25 (4), 646-647;
5. Colan, R., Viel, C.: Preparation of *N*-unsubstituted  $\beta$ -ketoamides by *Rhodococcus rhodochrous*-catalyzed hydration of  $\beta$ -ketonitriles, *Bulletin de la Société Chimique de France*, **1979**, 2, 362-365;
6. Breslow, R.: *Artificial Enzymes*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2005**;
7. Mohite, A.R., Bhat, R.G.: A practical and convenient protocol for the synthesis of (E)- $\alpha,\beta$ -unsaturated acids, *Organic Letter*, **2013**, 15 (17), 4564-4567;
8. Tietze, L.F.: Domino effects in organic chemistry, *Chemical Review*, **1996**, 96 (1), 115-136;
9. Kulp, S.S., Caldwell, C.B.: Reduction of  $\alpha,\beta$ -diarylacrylonitriles by sodium borohydride, *Journal of Organic Chemistry*, **1980**, 45 (1), 171-173;
10. Doré, J.C., Viel, C.: Antitumor chemotherapy. IX. Cytotoxic activity in cultured tumor cells of chalcone substituents and related compounds, *Journal de Pharmacie de Belgique*, **1974**, 29 (4), 341-351;
11. Das, D.D., Harlick, P.J.E., Sayari, A.: Applications of pore-expanded MCM-41 silica: 4. Synthesis of a highly active base catalyst, *Catalysis Communications*, **2007**, 8 (5), 829-833;
12. Suzuki, T.M., Yamamoto, M., Fukumoto, K., Akimoto, Y., Yano, K.: Investigation of pore-size effects on base catalysis using amino-functionalized monodispersed mesoporous silica spheres as a model catalyst, *Journal of Catalysis*, **2007**, 251 (2), 249-257;
13. Mondal, J., Modak, A., Bhaumik, A.: Highly efficient mesoporous base catalyzed Knoevenagel condensation of different aromatic aldehydes with malononitrile and subsequent noncatalytic Diels–Alder reactions, *Journal of Molecular Catalysis A: Chemical*, **2011**, 335 (1-2), 236-241;
14. Parida, K.M., Rath, D.: Amine functionalized MCM-41: Amine functionalized MCM-41: An active and reusable catalyst for Knoevenagel condensation reaction, *Journal of Molecular Catalysis A: Chemical*, **2009**, 310 (1-2), 93-100;
15. Gracia, M.D., Jurado, M.J., Luque, R., Campelo, J.M., Luna, D., Marinas, J.M., Romero, A.A.: Modified SBA-1 materials for the Knoevenagel condensation under microwave irradiation, *Microporous and Mesoporous Materials*, **2009**, 118 (1-3), 87-92;
16. Seo, Y.-H., Han, S.-C., Park, S.-E.: Amino functionalized silica nanotube for base catalyzed, *Studies in Surface Science and Catalysis*, **2008**, 174 (B), 1081-1086;
17. Macquarrie, D.J., Clark, J.H., Lambert, A., Mdoe, J.E.G., Priest, A.: Catalysis of the Knoevenagel reaction by  $\gamma$ -aminopropylsilica, *Reactive and Functional Polymers*, **1997**, 35 (3), 153-158;
18. Postole, G., Chowdhury, B., Karmakar, B., Pinki, K., Banerji, J., Auroux, A.: Knoevenagel condensation reaction over acid-base bifunctional nanocrystalline  $\text{Ce}_x\text{Zr}_{1-x}\text{O}_2$  solid solutions, *Journal of Catalysis*, **2010**, 269 (1), 110-121;



19. Zhang, Y., Zhao, Y.W., Xia, C.G.: Basic ionic liquids supported on hydroxyapatite-encapsulated  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanocrystallites: An efficient magnetic and recyclable heterogeneous catalyst for aqueous Knoevenagel condensation, *Journal of Molecular Catalysis A: Chemical*, **2009**, **306** (1-2), 107-112;
20. Dong, F., Li, Y.Q., Dai, R.F.: Knoevenagel condensation catalysed by poly (vinyl chloride) supported tetraethylenepentamine (PVC-TEPA), *Chinese Chemical Letters*, **2007**, **18** (3), 266-268;
21. Sebt, S., Tahir, R., Nazih, R., Saber, A., Boulaajaj, S.: Hydroxyapatite as new solid support for the Knoevenagel reaction in heterogeneous media without solvent, *Applied Catalysis A: General*, **2002**, **228** (1-2), 155-159;
22. Laspéras, M., Llorett, T., Chaves, L., Rodriguez, I., Cauvel, A., Brunel, D.: Amine functions linked to MCM-41-type silicas as a new class of solid base catalysts for condensation reactions, *Studies in Surface Science and Catalysis*, **1997**, **108**, 75-82;
23. Choi, Y., Kim, K.-S., Kim, J.-H., Seo, G.: Knoevenagel condensation between ethylcyanoacetate and benzaldehyde over base catalysts immobilized on mesoporous materials, *Studies in Surface Science and Catalysis*, **2001**, **135**, 139;
24. Gawande, M.B., Jayaram, R.V.: A novel catalyst for the Knoevenagel condensation of aldehydes with malononitrile and ethyl cyanoacetate under solvent free conditions, *Catalysis Communications*, **2006**, **7** (12), 931-935;
25. Kim, Y.C., Hart, H.: Synthesis and NMR spectra of 3-aryl-1,1,2,2-tetracyanocyclopropanes, *Tetrahedron*, **1969**, **25** (17), 3869-3877;
26. Kaupp, G., Naimi-Jamal, M.R., Schmeyers, J.: Solvent-free Knoevenagel condensations and Michael additions in the solid state and in the melt with quantitative yield, *Tetrahedron*, **2003**, **59** (21), 3753-3760;
27. Moussaoui, Y., Ben Salem, R.: Catalysed Knoevenagel reactions on inorganic solid supports: Application to the synthesis of coumarine compounds, *Comptes Rendus Chimie*, **2007**, **10** (12), 1162-1169;
28. Perlmutter, P.: *Conjugate Addition Reaction in Organic Synthesis*, Pergamon Press, Oxford (UK), **1992**, 114;
29. Nasarov, Saw' jallow: Synthesizing 3-(2,6-dioxo cyclohexyl)propanenitrile, *Zhurnal Obshchei Khimii*, **1954**, **24**, 469-472;
30. Mahajan, J.R.: Carbon-13 and proton magnetic resonance spectra of 2,2-dialkyl-5,5-dimethylcyclohexane-1,3-diones (2,2-dialkyldimedones), *Journal of the Chemical Society, Perkin Transactions 1*, **1978**, **11**, 1434-1437;
31. Greenhill, J.V., Mohamed, M.I.: Reactions between enaminones and enones. Part 1. Some unexpected products from the condensation of 3-aminocyclohexenones with methyl vinyl ketone, *Journal of the Chemical Society, Perkin Transactions 1*, **1979**, 1411-1414;
32. Halssall, T.G., McHale, P.J., Morales Mendez, A.: Rearrangement of epoxides. Part 2. The preparation and rearrangement of some epoxides of 2,2-dimethylbicyclo[4.3.0]non-1(9)-enes carrying substituents at C(3) and C(6), *Journal of the Chemical Society, Perkin Transactions 1*, **1978**, **12**, 1606-1618;
33. Brown, H.L., Buchanan, G.L., Curran, A.C.W., McLay, G.W.: The thermal-Michael reaction – I: Orientation features, *Tetrahedron*, **1968**, **24** (12), 4565-4571;
34. Walcarius, A., Etienne, M., Bessière, J.: Rate of access to the binding sites in organically modified silicates: 1. Amorphous silica gels grafted with amine or thiol groups, *Chemistry of Materials*, **2002**, **14** (6), 2757-2766.