Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 80 (10) 1265–1272 (2015)
JSCS–4794
UDC 547.75'81'77:542.913+544.351–145.82+546.284–31
Original scientific paper

Green one-pot, four-component synthesis of spiro[indoline-3,4′--pyrano[2,3-*c*]pyrazole] derivatives using amino-functionalized nanoporous silica SBA-15 under solvent-free conditions

GHODSI MOHAMMADI ZIARANI[1]*, MAHSHID RAHIMIFARD[1], FATEMEH NOURI[1] and ALIREZA BADIEI[2]

[1]*Department of Chemistry, Alzahra University, Vanak Square, P. O. Box 19938939973, Tehran, Iran and* [2]*School of Chemistry, College of Science, University of Tehran, Tehran, Iran*

(Received 30 September 2014, revised 18 May, accepted 24 May 2015)

Abstract: Propylamine functionalized nanoporous silica (SBA–Pr-NH_2) was used as an efficient heterogeneous solid basic nanoreactor in the synthesis of 6′-amino-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-one derivatives **5** through a one-pot, four-component condensation of isatin derivatives **1**, activated methylene reagents **2**, hydrazine hydrate **3** and *β*-keto esters **4** under solvent-free conditions at room temperature.

Keywords: amino-functionalized nanoporous silica; solvent-free; nanoporous silica; four components; one-pot; spiro indole; pyranopyrazole.

INTRODUCTION

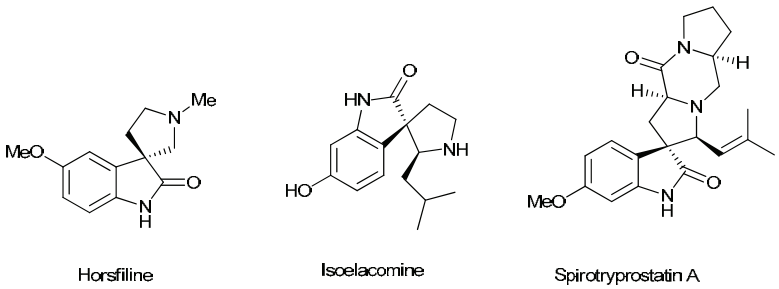
The indole ring is the core structure of many alkaloids, natural products and medicinal agents.[1] Compounds containing this moiety present a variety of antibacterial and antifungal activities.[2] In addition, it was reported that substitution of the indole ring with heterocycles at the 3-carbon position significantly improves biological properties.[3] The resulting spirooxindoles are found in various pharmaceutical components and natural products (Scheme 1).[4]

Heterocyclic compounds consisting of pyrano[2,3-*c*]pyrazoles with numerous biological properties, such as anticancer,[5] antibacterial,[6] antimicrobial,[7] anti-inflammatory,[8] ChK1 kinase inhibitors,[9] antifungal[10] and molluscicidal activity[11] occupy a special place in medicinal chemistry. Thus, considerable attention has been focused on the development of new modified methods for their synthesis.

Spiroindoline-pyranopyrazole derivatives can be obtained through various synthetic methods. Shestopalov *et al.* reported a four-component reaction for their synthesis by condensation of isatin, hydrazine, malononitrile and *β*-keto

* Corresponding author. E-mails: gmziarani@hotmail.com; gmohammadi@alzahra.ac.ir
doi: 10.2298/JSC140930045M

esters using triethylamine in ethanol under reflux conditions.[12] This reaction can also be affected using different catalysts, such as piperidine,[13,14] L-proline,[15] [DMBSI]HSO_4,[16] Mn(bpyo)$_2$/MCM-41,[17] Bmim(OH)/chitosan,[18] uncapped SnO_2 quantum dots,[19] 4-(dimethylamino)pyridine[20] and meglumine.[21] Another common synthetic method for the synthesis of this class of compounds is a three-component condensation of pyrazolone, malononitrile and isatin in the presence of catalysts such as triethylamine,[22] ZnS nanoparticles,[4] L-proline,[23] K_2CO_3,[24] triethanolamine[25] and $NaHCO_3$.[26] However these methods have some disadvantages, such as long reaction times, expensive and non-reusable catalysts and hard work-up or catalyst removal.



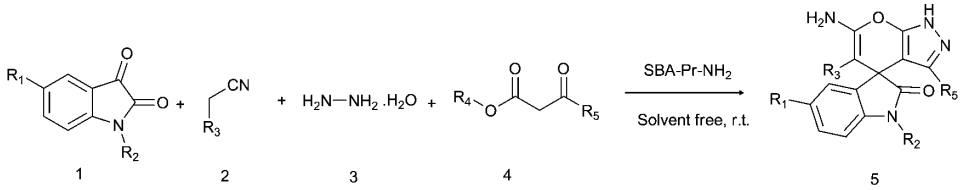
Scheme 1. Compounds with spirooxindole skeleton.

In recent years, mesoporous materials especially mesoporous silica, such as SBA-15 (Santa Barbara Amorphous), have attracted considerable attention. SBA-15 is a unique inorganic solid support with high surface area, large pore size and high thermal stability.[27] Grafting various organic compounds on the surface of SBA-15 could improve the catalytic activity of the silica surface. Amino functionalized SBA-15 (SBA–Pr-NH_2) was proved to be an efficient heterogeneous mesoporous solid base catalyst that could be used in the synthesis of various heterocyclic compounds.[28–30] In this work, an attempt was made to develop a modified methodology in the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives **5** using the green solid heterogeneous base nanocatalyst SBA–Pr-NH_2 under solvent free conditions at room temperature *via* a one-pot four-component condensation of isatin derivatives **1**, activated methylene reagents **2**, hydrazine hydrate **3** and *β*-keto esters **4.**

RESULTS AND DISCUSSION

This report is devoted to the study of the four component condensation of isatin derivatives **1**, activated methylene reagents (malononitrile or ethyl cyanoacetate) **2**, hydrazine hydrate **3** and *β*-keto esters **4** catalyzed by nanoporous base catalyst of SBA–Pr-NH_2 under solvent-free conditions at room temperature (Scheme 2). In initiation of this study, various conditions employing different solvents, such as ethanol or water, and a solvent-free system with or without catalyst at room temperature were evaluated. Among the tested conditions, the best

result was obtained in the presence of SBA–Pr-NH_2 using the solvent-free system at room temperature (Table I).



Scheme 2. Synthesis of 6′-amino-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-one derivatives **5** in the presence of SBA–Pr-NH_2.

TABLE I. The optimization of the reaction conditions in the synthesis of **5a** at room temperature

Entry	Catalyst	Solvent	*t* / h	Yield, %
1	–	EtOH	8	50
2	–	H_2O	3	50
3	SBA–Pr-NH_2	EtOH	2	70
4	SBA–Pr-NH_2	–	0.25	80

Under the optimized conditions, various 6′-amino-1′*H*-spiro[indoline-3,4′--pyrano[2,3-*c*]pyrazol]-2-one derivatives **5a**–**f** were synthesized in the presence of SBA–Pr-NH_2 using several isatin derivatives **1a**–**d**, activated methylene reagents **2a** and **b**, hydrazine hydrate **3** and *β*-keto esters **4a**–**c**. Results are summarized in Table II. Under these conditions, the reactions were realized easily to produce spiroindoline-pyranopyrazole derivatives in good yields. It should be noted that the presence of halogens on the reacting isatins (Entries 3 and 5) decreased the reaction time in comparison to that for to isatin (Entry 1). It may be related to inductive withdrawing effects of halogens on the carbonyl group of isatin. On the other hand, replacing malononitrile with ethyl cyanoacetate increased the reaction time, which was attributed to the competing formation of the Knoevenagel adduct of isatin and the activated methylene reagents.

TABLE II. Four-component synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives **5a**–**f** in the presence of SBA–Pr-NH_2

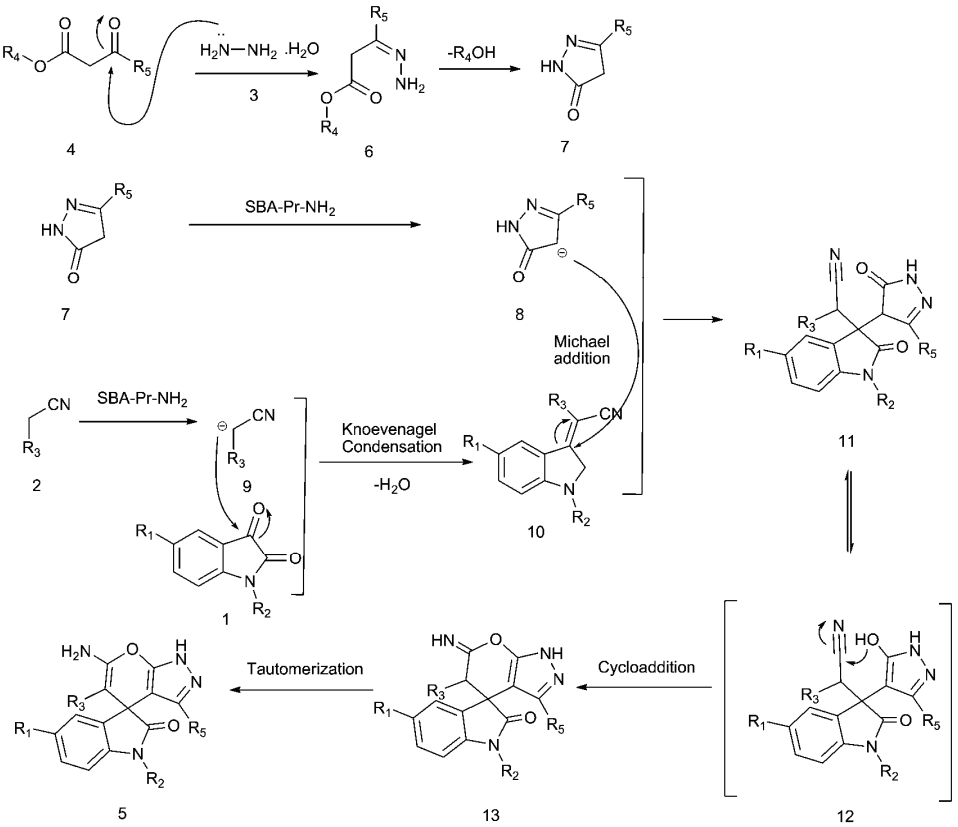
Entry	R_1	R_2	R_3	R_4	R_5	Product	*t* min	Yield %	M.p. range, °C	Literature m.p., °C
1	H	H	CN	Et	Me	**5a**	15	80	278–280	279–280[26]
2	H	H	CN	Me	Me	**5a**	15	87	278–280	279–280[26]
3	Br	H	CN	Et	Me	**5b**	10	85	281–283	282–283[26]
4	H	CH_2Ph	CN	Et	Me	**5c**	15	78	268–270	Not reported
5	Cl	H	CN	Et	Me	**5d**	10	83	296–298	297–298[15]
6	H	H	CN	Et	Ph	**5e**	15	85	279–281	280–281[13]
7	H	H	CO_2Et	Et	Me	**5f**	20	80	280–282	281–282[31]
8	H	H	CO_2Et	Me	Me	**5f**	25	83	280–282	281–282[31]

The reusability of the catalyst was investigated under the optimized conditions for the synthesis of the model compound **5a**. As shown in Table III, the recycling process was completed four times with no significant decrease in the catalyst activity. The yields for the four runs were found to be 80, 78, 78 and 76 %, respectively.

TABLE III. Synthesis of the spiroindoline–pyranopyrazole **5a** with recycled SBA–Pr-NH_2

Parameter	1st run	2nd run	3rd run	4th run
Time, min	15	15	20	20
Yield, %	80	78	78	76

A possible mechanism for synthesis of 6′-amino-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-one derivatives **5** is presented in Scheme 3. The initiation step begins with the two-component condensation of hydrazine hydrate **3** and *β*-keto esters **4** to afford the 5-alkyl-2,4-dihydro-3*H*-pyrazol-3-one **7**, which was deprotonated by SBA–Pr-NH_2. Then a fast Knoevenagel condensation occurred



Scheme 3. Plausible mechanism.

between isatin derivatives **1** and activated methylene reagents **2**. Michael addition of **8** to **10** afforded compound **11**, which was followed by enol–keto tautomerization to yield intermediate **12**. Addition of hydroxyl to cyano group provided compound **13**. Tautomerization of compound **13** yielded the desired product **5** (Scheme 3).

Several varying conditions have been reported in the literature for the synthesis of 6′-amino-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-one derivatives **5**, as given in Table IV.

TABLE IV. Comparison of several conditions

Entry	Catalyst	Solvent	Conditions	*t* / min	Yield, %	Year
1	$N(Et)_3$	EtOH	Reflux	5–30	76–85	2009[12]
2	Piperidine	H_2O	r.t.	300	80-97	2010[14]
3	Piperidine	EtOH	Ultrasound	60	73–93	2012[13]
4	$[DMBSI]HSO_4$	–	60 °C	1–2	88–96	2014[16]
5	$Mn(bpyo)_2$/MCM-41	H_2O	Reflux	18–24	89–92	2015[17]
6	Bmim(OH)/Chitosan		r.t.	150–210	89–93	2014[18]
7	Uncapped SnO_2 quantum dot	H_2O	r.t.	120–150	90–93	2014[19]
8	4-(Dimethylamino)pyridine	EtOH	60 °C	60	75–85	2014[20]
9	Meglumine	$EtOH/H_2O$	r.t.	27–35	90–93	2013[21]
10	L-proline	H_2O	80 °C	10–30	83–92	2013[15]
11	SBA–Pr-NH_2	–	r.t.	10–25	78–87	Present work

In the current method, the basic nanoreactor with hexagonal platelet morphology, several reusabilities, ease of handling and removal from the reaction medium could make it an economic and efficient green solid heterogeneous nanocatalyst for this synthesis. Furthermore, the short reaction time, solvent-free conditions, room temperature and simple procedure are other advantages of this method.

Structure of the catalyst

The surface of the catalyst was analyzed by different methods, such as TGA, FT-IR and others, which demonstrated that the organic groups (propylamine) were immobilized into the pores.[29]

The same ordered mesoscopic structured silica with (100), (110) and (200) reflections in the low-angle XRD patterns of SBA-15 and SBA–Pr-NH_2 indicated a two-dimensional hexagonal symmetrical array of nano-channels. This means that the structural integrity of SBA-15 was not affected during the functionalization reaction. Moreover, the TEM image of SBA–Pr-NH_2 confirmed the parallel channels were similar to the configuration of the pores in SBA-15. This indicated that during grafting of the aminopropyl-triethoxysilane (APTES) groups, the pores of SBA-15 did not collapse.[29]

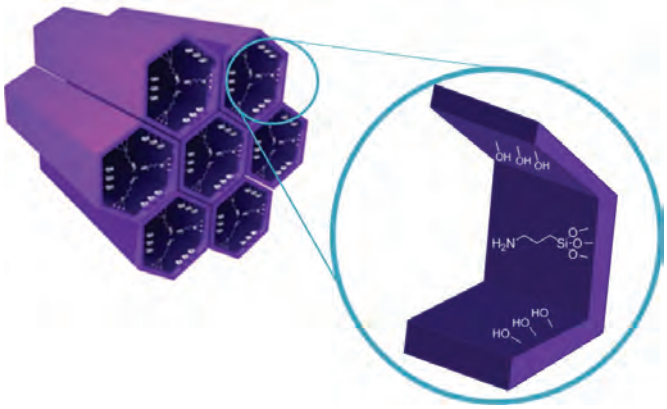


Fig. 1. Functionalized SBA-15.

EXPERIMENTAL

Materials and methods

The chemical compounds used in this work were all obtained from Merck and were employed without further purification. The IR spectra were recorded from KBr disks using a Fourier-transform (FT)-IR Bruker Tensor 27 instrument. The melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. ^{1}H- and ^{13}C-NMR were run on a Bruker DPX at 400 or 250 MHz using TMS as an internal standard. The mass spectra were obtained on an Agilent 5973 MS detector.

The physical, analytical and spectral data of compounds **5a**–**f** are given in the Supplementary material to this paper.

Synthesis and functionalization of SBA-15

The nanoporous compound SBA-15 was synthesized and functionalized according to a previous report. The triblock copolymer Pluronic P126 was used as the directing agent for the preparation of SBA-15 as nanoporous silica.[32,33] Functionalization of SBA-15 was performed through post-grafting of calcined SBA-15 with (3-aminopropyl)triethoxysilane (APTES, Fig. 1).[29]

*General procedure for the synthesis of the 6′-amino-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]-pyrazol]-2-one derivatives*

A suspension of SBA–Pr-NH_2 (0.02 g), isatin derivatives **1** (1 mmol), methylene reagent (malononitrile or ethyl cyanoacetate) **2** (1 mmol), hydrazine hydrate (80 %) **3** (1.4 mmol, 0.07 g) and *β*-keto ester **4** (1 mmol) was stirred at room temperature under solvent-free conditions for an appropriate time as indicated in Table II. Upon completion of the reaction as monitored by TLC (thin layer chromatography), the solid product was dissolved in hot ethyl acetate and the insoluble catalyst was removed by filtration. The filtrate was cooled to room temperature to yield pure crystals of a spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivative **5**.

CONCLUSION

In conclusion, amino-functionalized SBA-15 could serve as an efficient heterogeneous solid basic nanocatalyst for the synthesis of 6′-amino-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-one derivatives **5** at room

temperature and under solvent-free conditions. This procedure offers several advantages, such as short reaction times, mild reaction conditions, high yield of products, easy workup procedure, and reusability of the catalyst.

SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data of compounds **5a**–**f** are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. We gratefully acknowledge the financial support from the Research Council of Alzahra University and the University of Tehran.

ИЗВОД

ЗЕЛЕНА СИНТЕЗА ДЕРИВАТА СПИРО[ИНДОЛИН-3,4'-ПИРАНО[2,3-*c*]ПИРАЗОЛА], У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ, УПОТРЕБОМ АМИНО ФУНКЦИОНАЛИЗОВАНИХ НАНО-ЧЕСТИЦА СИЛИКА-ГЕЛА БЕЗ РАСТВАРАЧА

GHODSI MOHAMMADI ZIARANI[1], MAHSHID RAHIMIFARD[1], FATEMEH NOURI[1] и ALIREZA BADIEI[2]

[1]*Department of Chemistry, Alzahra University, Vanak Square, P. O. Box No. 19938939973, Tehran, Iran* и [2]*School of Chemistry, College of Science, University of Tehran, Tehran, Iran*

Нано-честице силика-гела функционализоване пропиламином употребљене су као ефикасан хетерогени нанореактор у синтези деривата 6'-амино-1'*H*-спиро[индолин-3,4'-пирано[2,3-*c*]пиразол]-2-она **5** у четворокомпонентној реакцији кондензације деривата изатина **1**, активних метиленских реагенаса **2**, хидразин-хидрата **3** и *β*-кето-естара **4** без присуства растварача, на собној температури.

(Примљено 30. септембра 2014, ревидирано 18. маја, прихваћено 24. маја 2015)

REFERENCES

1. R. Sundberg, *The Chemistry of Indoles*, Vol. 18, Elsevier, New York, USA, 2012, p. 431
2. T. C. Leboho, J. P. Michael, W. A. van Otterlo, S. F. van Vuuren, C. B. de Koning, *Bioorg. Med. Chem.* **19** (2009) 4948
3. A. Abdel-Rahman, E. Keshk, M. Hanna, S. M. El-Bady, *Bioorg. Med. Chem.* **12** (2004) 2483
4. A. Dandia, V. Parewa, A. K. Jain, K. S. Rathore, *Green Chem.* **13** (2011) 2135
5. J.-L. Wang, D. Liu, Z.-J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri, Z. Huang, *Proc. Natl. Acad. Sci. USA* **97** (2000) 7124
6. Z. Ren, W. Cao, W. Tong, Z. Jin, *Synth. Commun.* **35** (2005) 2509
7. E. El-Tamany, F. A. El-Shahed, B. H. Mohamed, *J. Serb. Chem. Soc.* **64** (1999) 9
8. M. E. Zaki, H. A. Soliman, O. A. Hiekal, A. E. Rashad, *Z. Naturforsch., C; J. Biosci.* **61** (2006) 1
9. N. Foloppe, L. M. Fisher, R. Howes, A. Potter, A. G. Robertson, A. E. Surgenor, *Bioorg. Med. Chem. Lett.* **14** (2006) 4792
10. M. B. Hogale, B. N. Pawar, *J. Indian Chem. Soc.* **66** (1989) 206
11. F. M. Abdelrazek, P. Metz, O. Kataeva, A. Jaeger, S. F. El-Mahrouky, *Arch. Pharm.* **340** (2007) 543
12. Y. M. Litvinov, A. A. Shestopalov, L. A. Rodinovskaya, A. M. Shestopalov, *J. Comb. Chem.* **11** (2009) 914
13. Y. Zou, Y. Hu, H. Liu, D. Shi, *ACS Comb. Sci.* **14** (2012) 38

14. S. Ahadi, Z. Yasaei, A. Bazgir, *J. Heterocycl. Chem.* **47** (2010) 1090
15. J. Yu, Y. Zhou, T. Shen, W. Mao, K. Chen, Q. Song, *J. Chem. Res.* **37** (2013) 365
16. M. Mamaghani, R. Hossein Nia, F. Shirini, K. Tabatabaeian, M. Rassa, *Med. Chem. Res.* **24** (2015) 1916
17. M. Daraie, Y. S. Beheshtiha, M. M. Heravi, *Monatsh. Chem.* **146** (2015) 191
18. P. Rai, M. Srivastava, J. Singh, J. Singh, *New J. Chem*. **38** (2014) 3181
19. S. Paul, K. Pradhan, S. Ghosh, S. De, A. R. Das, *Tetrahedron* **70** (2014) 6088
20. J. Feng, K. Ablajan, A. Sali, *Tetrahedron* **70** (2014) 484
21. R.-Y. Guo, Z.-M. An, L.-P. Mo, S.-T. Yang, H.-X. Liu, S.-X. Wang, Z.-H. Zhang, *Tetrahedron* **69** (2013) 9931
22. V. Y. Mortikov, Y. M. Litvinov, A. Shestopalov, L. Rodinovskaya, A. Shestopalov, *Russ. Chem. Bull.* **57** (2008) 2373
23. Y. Li, H. Chen, C. Shi, D. Shi, S. Ji, *J. Comb. Chem.* **12** (2010) 231
24. Y. Liu, D. Zhou, Z. Ren, W. Cao, J. Chen, H. Deng, Q. Gu, *J. Chem. Res.* **2009** (2009) 154
25. R. G. Redkin, L. A. Shemchuk, V. P. Chernykh, O. V. Shishkin, S. V. Shishkina, *Tetrahedron* **63** (2007) 11444
26. Y. Liu, Z. Ren, W. Cao, J. Chen, H. Deng, M. Shao, *Synth. Commun.* **41** (2011) 3620
27. K. Bahrami, M. M. Khodaei, P. Fattahpour, *Catal. Sci. Technol.* **1** (2011) 389
28. M. Mirza-Aghayan, N. Mohammadian, M. A. Malakshah, R. Boukherroub, A. Tarlani, *J. Iran. Chem. Soc.* **10** (2013) 559
29. G. Mohammadi Ziarani, A. Badiei, S. Mousavi, N. Lashgari, A. Shahbazi, *Chin. J. Catal.* **33** (2012) 1832
30. G. Mohammadi Ziarani, N. H. Mohtasham, N. Lashgari, A. Badiei, M. Amanlou, R. Bazl, *J. Nanostructure Chem.* **2** (2013) 489
31. E. A. A. Hafez, F. M. Abdul Galil, S. M. Sherif, M. H. Elnagdi, *J. Heterocycl. Chem.* **23** (1986) 1375
32. A. Shahbazi, H. Younesi, A. Badiei, *Chem. Eng. J.* **168** (2011) 505
33. A. Badiei, H. Goldooz, G. Mohammadi Ziarani, *Appl. Surf. Sci.* **257** (2011) 4912.