Scientific paper

Efficient Synthesis of Spironaphthopyrano [2,3-d]pyrimidine-5,3'-indolines under Solvent-free Conditions Catalyzed by SBA-Pr-SO_3H as a Nanoporous Acid Catalyst

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Abstract

A green, simple one-pot synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indoline derivatives by a three-component reaction of isatins, 2-naphthol, and barbituric acids under solvent-free conditions in the presence of SBA-Pr-SO_3H has been accomplished. Sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) as a heterogeneous nanoporous solid acid catalyst was found to be an efficient and recyclable acid catalyst in this synthesis.

Keywords: Spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indoline; Isatin; Barbituric acid; Functionalized SBA-15; Green synthesis

1. Introduction

Naphthopyrans constitute an important class of photochromic compounds which show great promise for this application.[1,2] They are also prevalent in numerous natural products with significant biological and medicinal properties.[3] Pyrimidine systems as important pharmacophors and potential drugs, have a unique place in medicinal chemistry[4] and possess various biological properties such as anti-HIV,[5] anti-tumor,[6] anti-inflammatory,[7] and anti malarial activities.[8] Pyrimidine nucleus is also present in vitamin B_2 and folic acid. Isatin series with their multifunctional compounds and diversity of possible transformations are versatile substrates that can be used in multicomponent reactions.[9] The indole nucleus is a fundamental constituent of a number of natural and synthetic products with important biological activity.[10,11] Besides, sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[12,13]

Considering these facts, in this work, we would like to report on our studies toward the synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines in the presence of SBA-Pr-SO_3H as a nano-reactor. There are only two reports on multicomponent entries to the synthesis of these heterocyclic moieties. Recently, Bazgir and coworkers reported a three-component cyclo-condensation reaction of isatins, 2-naphthol, and barbituric acids in the presence of catalytic *p*-toluenesulfonic acid in water medium.[14] An important disadvantage of this approach is a need for highly prolonged reaction times (24 h). This reaction was also carried out using ionic liquid [Hmim][HSO_4] in a solvent-free media (1–2 h).[15] However, there is still room for improvement in the present methods so as to overcome the disadvantage of long reaction times. In continuation of our studies on the application of heterogeneous solid catalysts in organic synthesis,[16–19] and since the development of a new methodology for the synthesis of these compounds which could be carried out under mild conditions and in a less time-consuming manner would be highly desirable, herein, we report an efficient and green protocol for the three-component synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indoli-

nes using SBA-Pr-SO_3H as a highly active nanoporous heterogeneous acid catalyst.

Recently, mesoporous solids having unique features such as high specific surface area, large pore volume, biocompatibility, and excellent stability have received considerable attention. Of the many different functionalized silica materials, sulfonic acid functionalized SBA-15 is one of the most important functionalized mesoporous materials that has been used in a variety of organic transformations.[20–23]

2. Experimental

2. 1. Materials and Instrumentations

The chemicals employed in this work were obtained from Merck Company and were used with no purifications. IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^{1}H NMR and ^{13}C NMR (300 MHz and 75 MHz) were run on a Bruker DPX, using TMS an internal standard (DMSO-d_6 solution). GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV while TEM was carried out on a Tecnai G^2 F30 at 300 kV.

2. 2. Synthesis of SBA-15-Pr-SO_3H

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report[16] and the modified SBA-Pr-SO_3H was used as a nanoporous solid acid catalyst in the following reaction.

2. 3. General Procedure for the Synthesis of Spironaphthopyrano[2,3-d] pyrimidine-5,3'-indoline (4a–j)

The SBA-Pr-SO_3H (0.02 g) was activated in vacuum at 100 °C and then after cooling to the room temperature, isatin **1** (0.29 g, 2 mmol), barbituric acid **2** (0.26 g, 2 mmol), and 2-naphthol **3** (0.28 g, 2 mmol), were added to it. The mixture was heated under solvent-free condition for the time reported in Table 2. Upon completion of the reaction, monitored by TLC, the generated solid product was dissolved in hot ethanol and DMF (15 mL), filtered to remove the undissolved catalyst and then the filtrate was cooled to afford the pure product **4a**. The catalyst was washed subsequently with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without significant loss of activity.

1,3-Dimethyl-5'-bromo-spiro[naphtha[1',2':5,6]pyrano[2,3-*d*]pyrimidine-5,3'-indoline]2,2',4(1*H*,3*H*)-trione (4f)

Gray solid, Yield: 69%, m.p. > 300 °C, IR (KBr) (ν_{max}, cm^{-1}): 3361, 2925, 1723, 1672, 1614. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (3H, s, CH_3), 3.70 (3H, s, CH_3), 7.19–8.06 (9H, m, ArH), 10.87 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) 23.6, 49.9, 81.6, 111.6, 119.1, 120.8, 121.7, 124.6, 126.0, 126.2, 127.3, 127.6, 128.0, 129.4, 129.7, 130.6, 131.0, 134.0, 146.0, 149.3, 149.9, 161.9, 177.8 ppm. Anal. Calcd for $C_{24}H_{16}BrN_3O_4$: C, 58.79; H, 3.29; N, 8.57. Found: C, 58.70; H, 3.22; N, 8.65%.

5'-Nitro-spiro[naphtha[1',2':5,6]pyrano[2,3-*d*]pyrimidine-5,3'-indoline]2,2',4(1*H*,3*H*)-trione (4g)

Gray solid, Yield: 78%, m.p. > 300 °C, IR (KBr) (ν_{max}, cm^{-1}): 3064, 2926, 1799, 1705, 1670. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35–8.08 (9H, m, ArH), 10.49 (1H, s, NH), 10.75 (1H, s, NH), 10.98 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) 49.9, 82.7, 111.5, 117.0, 120.0, 121.0, 124.0, 124.4, 126.6, 127.0, 127.7, 129.1, 129.6, 130.2, 131.0, 134.7, 146.1, 149.3, 149.8, 162.0, 178.2 ppm. MS (*m/z*, %): 428 (M$^+$, 6). Anal. Calcd for $C_{22}H_{12}N_4O_6$: C, 61.69; H, 2.82; N, 13.08. Found: C, 61.78; H, 2.90; N, 13.01%.

1,3-Dimethyl-5'-nitro-spiro[naphtha[1',2':5,6]pyrano[2,3-*d*]pyrimidine-5,3'-indoline]2,2',4(1*H*,3*H*)-trione (4h)

Gray solid, Yield: 63%, m.p. > 300 °C, IR (KBr) (ν_{max}, cm^{-1}): 3303, 2955, 1732, 1680, 1630. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.74 (3H, s, CH_3), 3.71 (3H, s, CH_3), 6.96–8.14 (9H, m, ArH), 10.50 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) 27.6, 47.7, 89.2, 109.4, 113.1, 116.1, 122.5, 122.9, 123.9, 126.2, 127.8, 128.7, 129.3, 130.4, 131.6, 131.9, 133.4, 144.3, 148.1, 149.9, 156.4, 162.6, 178.0 ppm. MS (*m/z*, %): 456 (M$^+$, 4). Anal. Calcd for $C_{24}H_{16}N_4O_6$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.23; H, 3.60; N, 12.34%.

5'-Chloro-spiro[naphtha[1',2':5,6]pyrano[2,3-*d*]pyrimidine-5,3'-indoline]2,2',4(1*H*,3*H*)-trione (4i)

Gray solid, Yield: 70%, m.p. > 300 °C, IR (KBr) (ν_{max}, cm^{-1}): 3310, 2927, 1790, 1710, 1654. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29–8.03 (10H, m, ArH), 9.88 (1H, s, NH), 10.83 (1H, s, NH), 10.07 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) 49.8, 82.7, 111.6, 115.1, 119.4, 120.8, 122.2, 124.6, 126.1, 127.6, 128.0, 129.0, 129.8, 130.6, 131.0, 132.2, 134.4, 145.9, 149.3, 149.8, 161.9, 177.9 ppm. MS (*m/z*, %): 417 (M$^+$, 4). Anal. Calcd for $C_{22}H_{12}ClN_3O_4$: C, 63.24; H, 2.89; N, 10.06. Found: C, 63.32; H, 2.80; N, 10.12%.

1,3-Dimethyl-5'-chloro-spiro[naphtha[1',2':5,6]pyrano[2,3-*d*]pyrimidine-5,3'-indoline]2,2',4(1*H*,3*H*)-trione (4j)

Gray solid, Yield: 70%, m.p. > 300 °C, IR (KBr) (ν_{max}, cm^{-1}): 3290, 1713, 1673, 1605. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.76 (3H, s, CH_3), 3.99 (3H, s, CH_3),

7.32–7.99 (9H, m, ArH), 10.01 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) 26.6, 48.3, 88.1, 108.4, 113.1, 117.1, 122.5, 122.7, 123.9, 125.2, 127.8, 128.7, 129.3, 130.5, 131.4, 131.5, 133.4, 144.3, 147.1, 149.1, 153.4, 161.6, 170.3, 177.0 ppm. MS (*m/z*, %): 445 (M^+, 6). Anal. Calcd for $C_{24}H_{16}ClN_3O_4$: C, 64.65; H, 3.62; N, 9.42. Found: C, 64.57; H, 3.53; N, 9.50%.

Table 1. Solvent effects on the synthesis of compound **4a.**

Entry	Solvent	Time (h)	Yield (%)[a]
1	EtOH	8	31
2	EtOH / H_2O	8	28
3	H_2O	5	32
4	MeCN	8	30
5	neat (140 °C)	15 min	80

[a] Isolated yield.

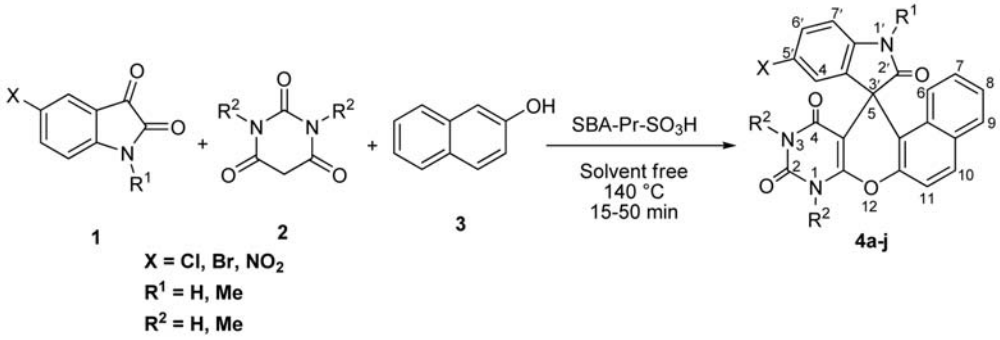
3. Results and Discussion

In this work, we would like to explore the catalytic activity of the sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) toward the clean one-pot synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines (Scheme 1). First, to study the solvent effects, we tested the reaction of isatin **1**, barbituric acid **2**, and 2-naphthol **3** as a simple model substrate in various solvents such as H_2O, MeCN, EtOH, and solvent-free system (Table 1). As results in Table 1 show, it was found that the yield of product **4a** was improved and the reaction time was shortened as the solvent-free system was employed as the reaction medium. We also examined this reaction in the absence of the catalyst and it was observed that the reaction did not occur without any catalyst.

Then, in regard to a library construction, this methodology was evaluated by using different isatins and barbituric acids. The results are summarized in the Table 2. Corresponding products were synthesized in good yields and appropriate times at 140 °C in the absence of any solvent.

After completion of the reaction (monitored by TLC), the crude product was dissolved in hot ethanol and DMF, the heterogeneous solid catalyst was removed easily by simple filtration, and after cooling the filtrate, the pure crystals of products were obtained. The acid catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone, and then reused for several times without significant loss of activity.

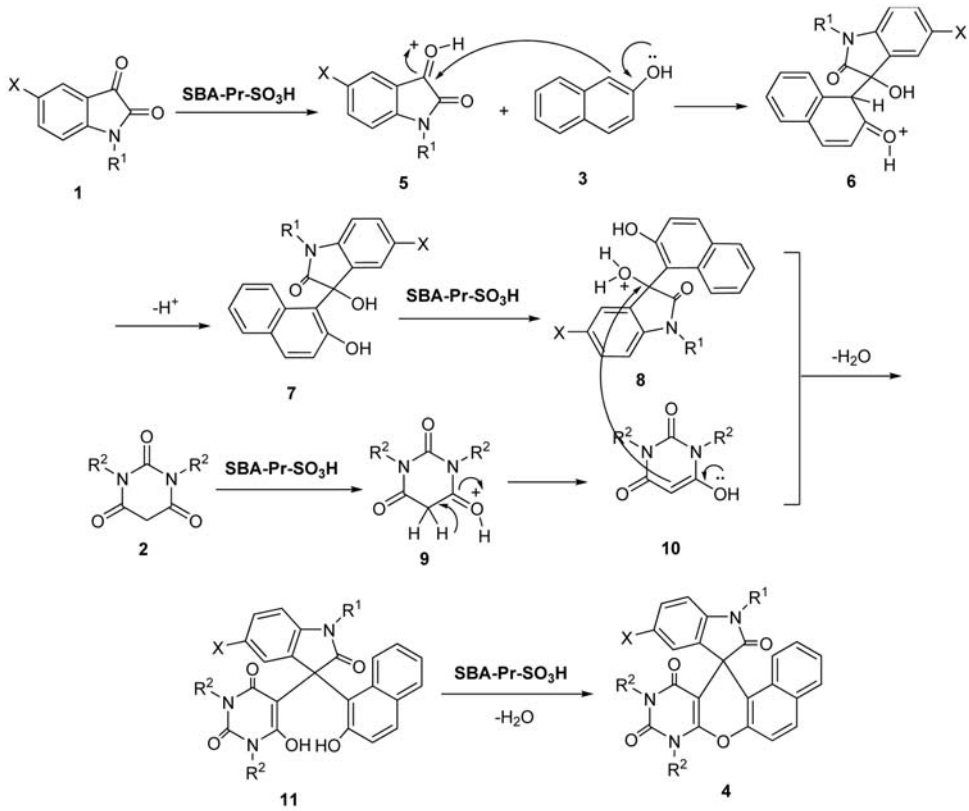
Compounds **4f–j** were new and their structures were deduced by elemental and spectral analysis. Melting points of known compounds **4a–e** were compared with reported values in the literature as shown in Table 2.



Scheme 1. Synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines **4** in the presence of SBA-Pr-SO_3H.

Table 2. SBA-Pr-SO_3H catalyzed the synthesis of products **4a–j** under solvent-free conditions.

Entry	X	R^1	R^2	Product	Time (min)	Yield (%)	M.p. (°C) Found	M.p. (°C) Reported
1	H	H	H	**4a**	15	80	>300	>300 [14]
2	H	H	Me	**4b**	20	75	>300	>300 [14]
3	H	Me	H	**4c**	15	84	>300	>300 [14]
4	H	Me	Me	**4d**	15	88	>300	>300 [14]
5	Br	H	H	**4e**	40	77	>300	>300 [14]
6	Br	H	Me	**4f**	35	69	>300	New
7	NO_2	H	H	**4g**	45	78	>300	New
8	NO_2	H	Me	**4h**	45	63	>300	New
9	Cl	H	H	**4i**	50	70	>300	New
10	Cl	H	Me	**4j**	25	70	>300	New



Scheme 2. Proposed mechanism for the synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines **4**

The most probable mechanism for this reaction is shown in Scheme 2. After protonation of carbonyl group of isatin **1** by the solid acid catalyst, a condensation occurs between compound **1** and 2-naphthol **3** to afford the intermediate **6**. Then, a subsequent addition of barbituric acid **2** to the intermediate **8**, followed by a cyclization and dehydration provides the desired product **4** (Scheme 2).

The SBA-15 as a nanoporous silica can be prepared by using commercially available triblock copolymer Pluronic P126 as a structure directing agent.[24,25] Integration of acidic functional groups (*e.g.*, $–SO_3H$) into SBA-15 has been explored to produce promising solid acids. The sulfonic acid functionalized SBA-15 was usually synthesized via a direct synthesis or post-grafting.[26,27] A schematic illustration for the preparation of SBA-Pr-SO_3H is shown in Figure 1. First, the calcined SBA-15 silica was functionalized with (3-mercaptopropyl)trimethoxy silane (MPTS) and then, the thiol groups were oxidized to sulfonic acid by hydrogen peroxide. The surface of the catalyst was analyzed by different methods such as TGA, BET and other methods which have confirmed that the organic groups (propyl sulfonic acid) were immobilized into the pores.[16]

The texture properties of SBA-15 and SBA-Pr-SO_3H are given in Table 3. The surface area, average pore diameter calculated by the BET method and pore volume of SBA-Pr-SO_3H are 440 m^2g^{-1}, 6.0 nm and 0.660 cm^3 g^{-1}, respectively, which are smaller than those of SBA-15 due to the immobilization of sulfonosilane groups into the pores.

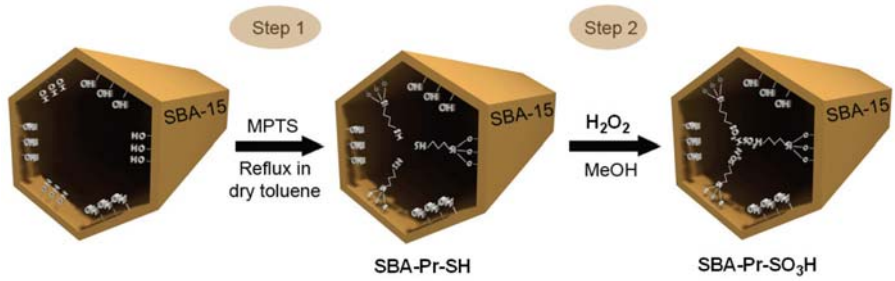


Figure 1. Schematic illustration for the preparation of SBA-Pr-SO_3H.

Table 3. Porosimetery values for SBA-15 and functionalized SBA-15.

	Surface area (cm^2g^{-1})	Pore volume (cm^3g^{-1})	Pore diameter (nm)
SBA-15	649	0.806	6.2
SBA-Pr-SO_3H	440	0.660	6.0

Figure 2 illustrates the SEM and TEM images of SBA-Pr-SO_3H. The SEM image (Figure 2a) shows uniform particles about 1 μm. The same morphology was observed for SBA-15. It can be concluded that morphology of the solid was preserved without a change during the surface modifications. On the other hand, the TEM image (Figure 2b) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pores of SBA-Pr-SO_3H have not collapsed during the two-steps reactions.

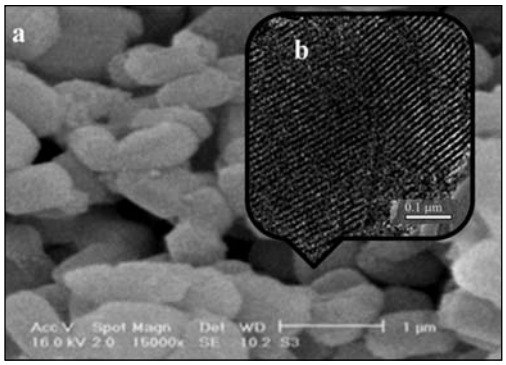


Figure 2. SEM image (a) and TEM image (b) of SBA-Pr-SO_3H.

4. Conclusions

In conclusion, we believe that this eco-friendly, solvent free procedure is advantageous for the simple and green one-pot preparation of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines. The use of SBA-Pr-SO_3H as a nano acid catalyst in this method generates the corresponding products in high yields under short reaction times and makes this procedure highly efficient and convenient. The green catalytic system can be reused several times with no significant decreases in yields and reaction rates.

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6. References

1. S. Nakatsuji, *Chem. Soc. Rev.* **2004**, *33*, 348–353.
2. B. Moine, G. Buntinx, O. Poizat, J. Rehault, C. Moustrou, A. Samat, *J. Phys. Org. Chem.* **2007**, *20,* 936–943.
3. A. A. Hussein, I. Barberena, T. L. Capson, T. A. Kursar, P. D. Coley, P. N. Solis, M. P. Gupta, *J. Nat. Prod.* **2004**, *67,* 451–453.
4. I. M. Lagoja, *Chem. Biodivers.* **2005**, *2,* 1–50.
5. A. Miazga, P. Ziemkowski, M. A. Siwecka, A. Lipniacki, A. Piasek, T. Kulikowski, *Nucleosides, Nucleotides, Nucleic Acids* **2010**, *29,* 438–444.
6. A. F. Cook, M. J. Holman, M. J. Kramer, P. W. Trown, *J. Med. Chem.* **1979**, *22,* 1330–1335.
7. M. S. Mohamed, S. M. Awad, A. I. Sayed, *Molecules* **2010**, *15,* 1882–1890.
8. M. A. Phillips, P. K. Rathod, *Infect. Disord. Drug Targets* **2010**, *10,* 226–239.
9. N. Lashgari, G. Mohammadi Ziarani, *Arkivoc* **2012**, *1,* 277–320.
10. W. Gul, M. T. Hamann, *Life Sci.* **2005**, 78, 442–453.
11. U. Pindur, T. Lemster, *Curr. Med. Chem.* **2001**, *8,* 1681–1698.
12. A. H. Abdel-Rahman, E. M. Keshk, M. A. Hanna, S. M. El-Bady, *Bioorg. Med. Chem.* **2004**, *12,* 2483–2488.
13. J. F. M. Da Silva, S. J. Garden, A. C. Pinto, *J. Braz. Chem. Soc.* **2001**, *12,* 273–324.
14. R. Ghahremanzadeh, T. Amanpour, M. Sayyafi, A. Bazgir, *J. Heterocycl. Chem.* **2010**, *47,* 421–424.
15. X. Yang, L. Yang, L. Wu, *Bull. Korean Chem. Soc.* **2012**, *33,* 714–716.
16. G. Mohammadi Ziarani, A. R. Badiei, Y. Khaniania, M. Haddadpour, *Iran. J. Chem. Chem. Eng.* **2010**, *29,* 1–10.
17. N. Lashgari, G. Mohammadi Ziarani, A. Badiei, P. Gholamzadeh, *Eur. J. Chem.* **2012**, *3,* 310–313.
18. G. Mohammadi Ziarani, A. Badiei, S. Mousavi, N. Lashgari, A. Shahbazi, *Chin. J. Catal.* **2012**, *33,* 1832–1839.
19. G. Mohammadi Ziarani, N. Lashgari, A. Badiei, M. Shakiba, *Chemija* **2013**, *24,* 142–150.
20. R. I. Kureshy, I. Ahmad, K. Pathak, N. H. Khan, S. H. R. Abdi, R. V. Jasra, *Catal. Commun.* **2009**, *10,* 572–575.
21. M. A. Naik, D. Sachdev, A. Dubey, *Catal. Commun.* **2010**, *11,* 1148–1153.
22. K. Bahrami, M. M. Khodaei, P. Fattahpour, *Catal. Sci. Technol.* **2011**, *1,* 389–393.
23. X. Shi, Y. Wu, H. Yi, G. Rui, P. Li, M. Yang, G. Wang, *Energies* **2011**, *4,* 669–684.
24. D. Zhao, Q. Huo, J. Feng, B. F. Chmelka, G. D. Stucky, *J. Am. Chem. Soc.* **1998**, *120,* 6024–6036.
25. D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279,* 548–552.
26. M. H. Lim, C. F. Blanford, A. Stein, *Chem. Mater.* **1998**, *10,* 467–470.
27. A. P. Wight, M. E. Davis, *Chem. Rev.* **2002**, *102,* 3589–3614.

Povzetek

Predstavljamo enostavno, »one-pot« sintezo spironaftopirano[2,3-*d*]pirimidin-5,3'-indolinskih derivatov, ki poteka skladno z zahtevami zelene kemije. Kot izhodne spojine za to trokomponentno sintezo smo uporabili izatine, 2-naftol in barbiturno kislino pod reakcijskimi pogoji brez uporabe topil in v prisotnosti SBA-Pr-SO_3H. SBA-15 funkcionaliziran s sulfonsko kislino (SBA-Pr-SO_3H) je heterogeni nanoporozni trdni kislinski katalizator, za katerega je bilo ugotovljeno, da je zelo učinkovit kislinski katalizator in da ga je mogoče enostavno reciklirati.