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آموزش مهارت های کاربردی در تدوین و چاپ مقاله

An Efficient Green Approach for the Synthesis of Structurally Diversified Spirooxindoles Using Sulfonic Acid Functionalized Nanoporous Silica (SBA-Pr-SO₃H)

Mohammadi Ziarani, Ghodsi*[†]; Aleali, Faezeh

Department of Chemistry, Alzahra University, P.O. Box 1993891176 Tehran, I.R. IRAN

Lashgari, Negar; Badiei, Alireza

School of Chemistry, University of Tehran, P.O. Box 14155-6455 Tehran, I.R. IRAN

ABSTRACT: One-pot multicomponent reaction between isatin, barbituric acid, and 6-amino-1,3-dimethyl uracil was investigated in the presence of sulfonic acid functionalized nanoporous silica (SBA-Pr-SO₃H) and resulted in the formation of spirooxindole dipyrimidines. Spirooxindole unit is found in many natural products and biologically active molecules and 1,4-dihydropyridines are an important class of compounds with interesting biological activities such as vasolidator, antitumor, antidiabetic, bronchodilator and anti-atherosclerotic activities. Excellent yields and short reaction times are related to the high efficiency of SBA-Pr-SO₃H that the reactions take place easily in its nano-pores. Mild reaction conditions and easy work-up procedures are other advantages of this green method.

KEY WORDS: Nano-reactor; Functionalized SBA-15; Spirooxindole dipyrimidines; Isatin; Barbituric acid.

INTRODUCTION

Multi component reactions (MCRs) are one group of the best tools for synthetic chemists to generate heterocyclic compounds in an atom- and time-efficient manner. Such reactions constitute an especially attractive synthetic strategy since they often shorten reaction periods, giving high overall chemical yields, and therefore can reduce the use of energy and manpower [1, 2]. MCRs are useful for the expedient creation of chemical libraries like spirooxindoles [3-5]. Spirooxindole unit as a privileged heterocyclic motif is found in many natural products and biologically active molecules [6-8]. Therefore, a number

of methods have been reported for the preparation of spirooxindole derivatives [9-11]. On the other hand, 1,4-dihydropyridines are an important class of compounds with interesting biological activities such as vasolidator [12], antitumor [13], antidiabetic [14], bronchodilator and anti-atherosclerotic activities [15].

In recent times, there has been increased interest on mesoporous silica materials as catalyst supports in heterogeneous catalysis because of their environmental compatibility, reusability, operational simplicity, and ease of isolation of the products [16, 17]. In this context,

* To whom correspondence should be addressed.

+ E-mail: gmziarani@hotmail.com , gmohammadi@alzahra.ac.ir
1021-9986/16/1/17 7/\$/2.70

SBA-15 (Santa Barbara Amorphous) is a kind of mesoporous silica featured by a well-ordered hexagonal structure, large pore size, high surface area, great pore wall thickness, and high thermal stability, which can conveniently include functional groups into its mesoporous framework to create efficient solid catalysts with improved catalytic properties as compared to conventional homogeneous and heterogeneous catalysts [18]. Basically there are two methods to anchor organic groups to a mesostructured silica surface: post-synthesis or grafting method and direct synthesis or co-condensation method [19, 20].

Herein, in continuation of our studies toward using nanoporous solid catalysts in organic reactions [21-25], the sulfonic acid functionalized SBA-15 was synthesized through post-grafting method and its catalytic activity was investigated in the synthesis of spirooxindole derivatives.

EXPERIMENTAL SECTION

The chemicals employed in this work were obtained from Merck Company and used without further purifications. IR spectra were recorded from KBr disk using an FT-IR Bruker Tensor 27 instrument. Melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. The ^1H and ^{13}C NMR were run on a Bruker DPX at 250 and 62.5 MHz, respectively using TMS as 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 G² F30 at 300 Kv.

Synthesis and functionalization of SBA-15

According to our previous report [26], the nanoporous compound SBA-15 was synthesized and functionalized and the modified SBA-Pr-SO₃H was used as a nanoporous solid acid catalyst in the following reaction.

General procedure for the synthesis of compound 4a, 1,3-dimethyl-1'H-spiro[indoline-3,5'-pyrido[2,3-d:6,5-d']dipyrimidine]-2,2',4,6',8'(3'H,7'H,9'H,10'H)-pentaone 4a

A mixture of barbituric acid (1 mmol, 0.128 g), isatin (1 mmol, 0.147 g), 6-amino-1,3-dimethyl uracil (1 mmol, 0.155 g) and SBA-Pr-SO₃H (0.02 g) was refluxed in water (4 mL) for the appropriated length of time,

as mentioned in Table 2. After completion of the reaction, as indicated by TLC, the generated solid product was dissolved in hot dimethylformamide (DMF), filtered for removing the catalyst and then the filtrate was cooled to afford the pure product. The catalyst was washed subsequently with diluted acid solution, distilled water and then acetone, dried under vacuum and reused several times without significant loss of activity. The spectra data of new compounds are given below:

5-Chloro-1',3',7',9'- tetramethyl -1'H- spiro[indoline-3,5'-pyrido[2,3-d:6,5-d']dipyrimidine]-2,2',4,6',8'(3'H,7'H,9'H,10'H)-pentaone (4e)

Yield: 92 %. M.p. >300 °C, IR (KBr): 3455, 3281, 3199, 1697, 1648, 1532, 1484, 1440, 1389, 1305, 1255, 1173, 1095, 1056, 995, 957, 776, 753, 506 cm⁻¹. ^1H NMR (250 MHz, DMSO- d_6): δ 3.00 (s, 3H, CH₃), 3.06 (s, 3H, CH₃), 3.38 (s, 3H, CH₃), 3.47 (s, 3H, CH₃), 7.01 (s, 1H, ArH), 7.22-7.32 (m, 2H, ArH), 9.46 (s, 1H, NH), 11.6 (s, 1H, NH) ppm. MS: m/z (%): 456 (M⁺, 47), 458 (M+2, 16), 428 (57), 412 (65), 382 (100).

1',3',7',9'-Tetramethyl-1'H-spiro[indoline-3,5'-pyrido [2,3-d:6,5-d']dipyrimidine] -2,2',4,6',8' (3'H,7'H,9'H,10'H)-pentaone (4f)

Yield: 94 %. M.p. >300 °C, IR (KBr): 3448, 3282, 3199, 1699, 1647, 1538, 1493, 1429, 1366, 1317, 1258, 1175, 995, 759, 673, 507 cm⁻¹. ^1H NMR (250 MHz, DMSO- d_6): δ 2.99 (s, 3H, CH₃), 3.07 (s, 3H, CH₃), 3.37 (s, 3H, CH₃), 3.45 (s, 3H, CH₃), 6.95 (m, 2H, ArH), 7.17-7.25 (m, 2H, ArH), 9.34 (s, 1H, NH), 11.57 (s, 1H, NH) ppm. ^{13}C NMR (62.5 MHz, DMSO- d_6): δ 27.4, 27.8, 30.5, 31.6, 51.3, 83.1, 97.7, 117.2, 121.3, 124.1, 126.6, 128.5, 136.0, 146.4, 150.7, 151.5, 152.5, 157.2, 160.2, 181.7 ppm. MS: m/z (%): 422 (M⁺, 16), 269 (33), 43 (100).

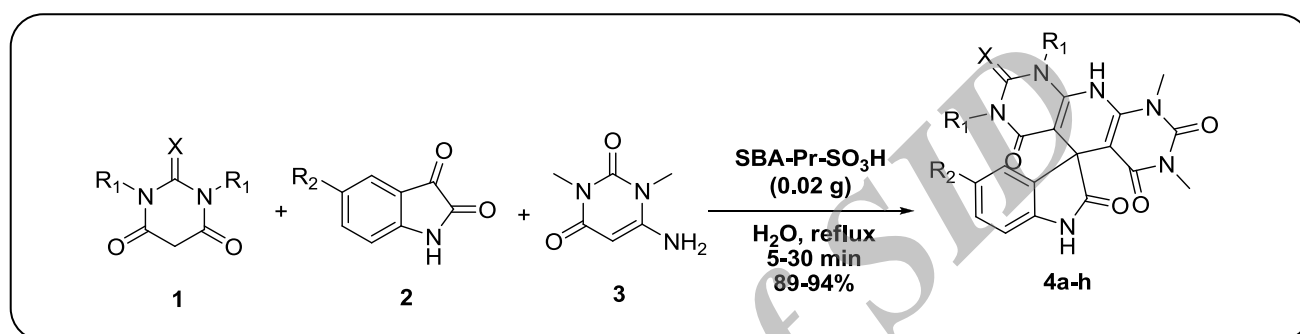
5-Fluoro -1',3',7',9'- tetramethyl -1'H-spiro[indoline-3,5'-pyrido[2,3-d:6,5-d']dipyrimidine]-2,2',4,6',8'(3'H,7'H,9'H,10'H)-pentaone (4g)

Yield: 93 %. M.p. >300 °C, IR (KBr): 3477, 3281, 1697, 1649, 1543, 1495, 1364, 1301, 1257, 1220, 1100, 1039, 995, 880, 776, 508 cm⁻¹. ^1H NMR (250 MHz, DMSO- d_6): δ 3.00 (s, 3H, CH₃), 3.07 (s, 3H, CH₃), 3.38 (s, 3H, CH₃), 3.47 (s, 3H, CH₃), 6.87 (dd, J = 2.5, 9.5, 1H, ArH), 7.03-7.11 (m, 1H, ArH), 7.28-7.34 (m, 1H, ArH), 9.39 (s, 1H, NH), 11.56 (s, 1H, NH) ppm. ^{13}C NMR (62.5 MHz,

Table 1: The optimization of reaction condition in the synthesis of spirooxindole dipyrimidine 4a.^a

| Entry | solvent | Temperature (°C) | Time (min) | Yield (%) ^b |
|-------|-----------------------------|------------------|------------|------------------------|
| 1 | EtOH | reflux | 15 | 81 |
| 2 | H ₂ O | reflux | 10 | 90 |
| 3 | EtOH/H ₂ O (2:1) | reflux | 15 | 79 |
| 4 | Neat | 140 °C | 20 | 50 |
| 5 | H ₂ O | r.t. | 45 | 30 |

a) Reaction conditions: barbituric acid (1 mmol), isatin (1 mmol), 6-amino-1,3-dimethyl uracil (1 mmol), and SBA-Pr-SO₃H (0.02 g). b) Isolated yield

**Scheme 1: Synthesis of spirooxindole dipyrimidines 4a-h.**

DMSO-*d*₆): δ 27.4, 27.8, 30.5, 31.6, 51.5, 97.2, 112.8, 113.1, 115.7, 116.0, 118.9, 122.9, 123.0, 132.7, 146.4, 150.7, 151.5, 152.9, 157.2, 160.2, 160.8, 181.4 ppm. MS: *m/z* (%): 440 (*M*⁺, 12), 286 (33), 69 (84), 43 (100).

5-Nitro -1',3',7',9'- tetramethyl -1'*H*-spiro[indoline-3,5'-pyrido[2,3-*d*:6,5-*d'*]dipyrimidine]-2,2',4',6',8'(3'*H*,7'*H*,9'*H*,10'*H*)-pentaone (4*h*)

Yield: 92 %. M.p. >300 °C, IR (KBr): 3450, 2924, 1705, 1647, 1540, 1511, 1332, 1262, 1173, 1106, 990, 845, 750, 669, 504 cm⁻¹. ¹H NMR (250 MHz, DMSO-*d*₆): δ 2.98 (s, 1H, CH₃), 3.08 (s, 1H, CH₃), 3.40 (s, 1H, CH₃), 3.52 (s, 1H, CH₃), 7.50 (d, *J*=9 Hz, 1H, ArH), 7.73 (d, *J*=1.7, 1H, ArH), 8.08 (dd, *J*=2.1, 8.7 Hz, 1H, ArH) ppm. ¹³C NMR (62.5 MHz, DMSO-*d*₆): δ 27.4, 28.0, 30.8, 31.8, 51.0, 84.0, 97.8, 117.9, 122.2, 122.8, 124.6, 142.0, 143.4, 146.0, 150.5, 151.4, 152.7, 157.3, 160.1, 181.2 ppm. MS: *m/z* (%): 267 (*M*⁺, 0.4), 118 (32), 73 (84), 44 (100).

RESULTS AND DISCUSSION

In this paper, we wish to report our results on the one-pot three-component condensation of barbituric acids **1**, isatins **2**, and 6-amino-1,3-dimethyl uracil **3** in the

presence of nanoporous solid acid catalyst (SBA-Pr-SO₃H) for the preparation of spirooxindole dipyrimidines **4a-h** (Scheme 1). In order to achieve optimum conditions, we initially investigated the reaction of barbituric acid **1**, isatin **2**, and 6-amino-1,3-dimethyl uracil **3** as a model reaction in the presence of various solvents such as H₂O, EtOH, EtOH/H₂O (2:1) and solvent-free condition. As shown results in Table 1, it was found that water is the most effective solvent for this reaction that affords the desired product in 10 minutes with high yield (90%). It was reported that in the absence of any catalyst, the product was obtained after 24 h in trace amount [27]. Then, in regard to library construction, this reaction condition was developed with three types of barbituric acids, five types of substituted isatins, and 6-amino-1,3-dimethyl uracil in a molar ratio of (1:1:1). Corresponding spirooxindole dipyrimidines were successfully prepared in 89-94%. The results are summarized in Table 2. Melting points of known products were compared with reported values in the literature as shown in Table 2. The high yields of reactions are related to the effect of a nanopore size about 6 nm of solid acid catalyst which acts as nano-reactor.

Table 2: SBA-Pr-SO₃H catalyzed three-component condensation of barbituric acids, isatins, and 6-amino-1,3-dimethyl uracil.

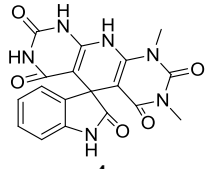
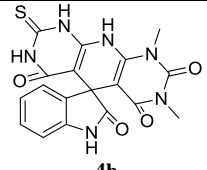
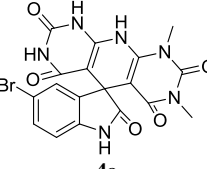
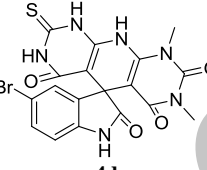
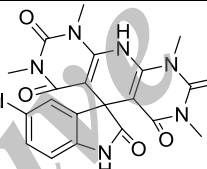
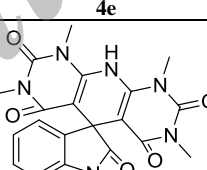
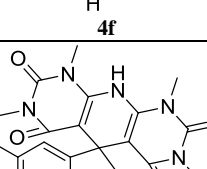
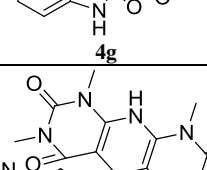
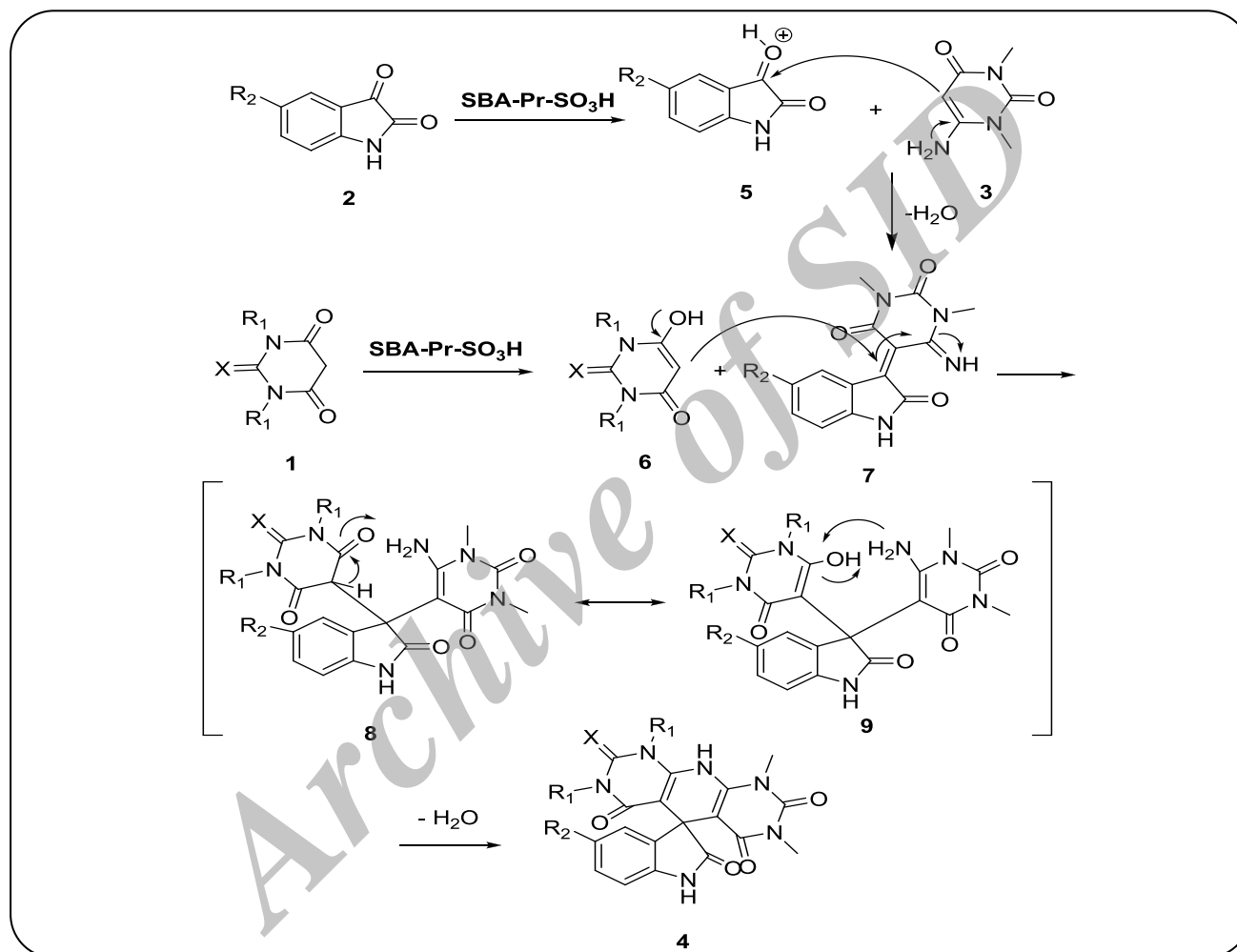
| Entry | R ₁ | R ₂ | X | Product | Time (min) | Yield (%) | Mp (°C) | Mp (Lit.) |
|-------|----------------|-----------------|---|---|------------|-----------|---------|-----------|
| 1 | H | H | O |  4a | 10 | 90 | >300 | >300 [27] |
| 2 | H | H | S |  4b | 20 | 89 | >300 | >300 [27] |
| 3 | H | Br | O |  4c | 15 | 91 | >300 | >300 [27] |
| 4 | H | Br | S |  4d | 30 | 89 | >300 | >300 [27] |
| 5 | Me | Cl | O |  4e | 8 | 92 | >300 | New |
| 6 | Me | H | O |  4f | 5 | 94 | >300 | New |
| 7 | Me | F | O |  4g | 5 | 93 | >300 | New |
| 8 | Me | NO ₂ | O |  4h | 5 | 92 | >300 | New |

Table 3: Comparison of different conditions in the synthesis of spirooxindole dipyrimidine 4a.

| Entry | Catalyst | Solvent | Condition | Time (h) | Yield (%) | Year |
|-------|--------------------------|------------------|-----------------|----------|-----------|-----------|
| 1 | PEG-OSO ₃ H | H ₂ O | Heating (70 °C) | 2 | 95 | 2013 [28] |
| 2 | SSLP ^a | H ₂ O | Heating (80 °C) | 30 min | 96 | 2013 [29] |
| 3 | nano-MSAIL ^b | H ₂ O | Stir.(r.t.) | 5 | 88 | 2013 [27] |
| 4 | SBA-Pr-SO ₃ H | H ₂ O | Reflux | 10 min | 90 | This work |

a) SSLP= silica-supported organocatalyst based on L-proline.

b) nano-MSAIL= nanometer scale, magnetic, supported, acidic ionic liquid.



Scheme 2: Proposed mechanism for the synthesis of spirooxindole dipyrimidines 4 in the presence of SBA-Pr-SO₃H.

The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature; the resulting solid product was dissolved in hot dimethylformamide (DMF), and after filtration of catalyst and cooling of the filtrate, the pure crystals of spirooxindole dipyrimidines were obtained.

Table 3 illustrates a comparison of the effectiveness of various catalysts used in the synthesis of spirooxindole dipyrimidines. It is clear from Table 3 that the current method is more efficient and less time-consuming, when compared with other existing methods.

The suggested mechanism for the SBA-Pr-SO₃H catalyzed formation of the product 4 is shown in Scheme 2.

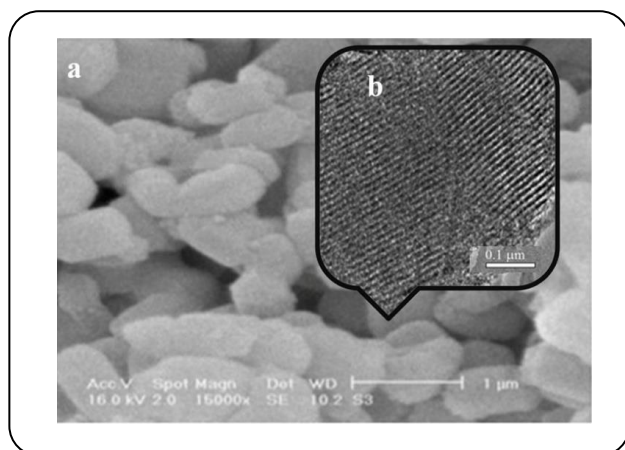


Fig. 1: SEM image (a) and TEM image (b) of SBA-Pr-SO₃H.

Protonation of a carbonyl group of isatin **2** by the solid acid catalyst activates it toward nucleophilic attack of 6-amino-1,3-dimethyl uracil **3** to yield intermediate **7**. Subsequently, the tautomerized barbituric acid **6** endures nucleophilic attack to **7** and gives the Michael adduct **8**. The intermediate **8** tautomerizes to generate intermediate **9**. Subsequent cyclization and elimination of water affords the corresponding spirooxindole dipyrimidine **4**.

Fig. 1 shows the SEM and TEM images of SBA-Pr-SO₃H. SEM image (Fig. 1, a) illustrates uniform particles about 1 μm which the same morphology was observed for SBA-15 and TEM image (Fig. 1, b) demonstrated parallel channels, that resemble the pore configurations of SBA-15.

CONCLUSIONS

In conclusion, we have successfully developed a simple green method for the synthesis of spirooxindole dipyrimidines through the reaction of isatins, barbituric acids, and 6-amino-1,3-dimethyl uracil in the presence of a catalytic amount of SBA-Pr-SO₃H. Among the advantages of this new method are excellent yields, short reaction times, environmental friendliness, operational simplicity, and using SBA-Pr-SO₃H as an efficient nano-reactor that the reaction proceeds easily in its nano-pores.

Acknowledgements

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

Received : Mar. 15, 2015 ; Accepted : Jul. 17, 2015

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کارگاه های آموزشی مرکز اطلاعات علمی



مقاله نویسی علوم انسانی



اصول تنظیم قراردادها



آموزش مهارت های کاربردی در تدوین و چاپ مقاله