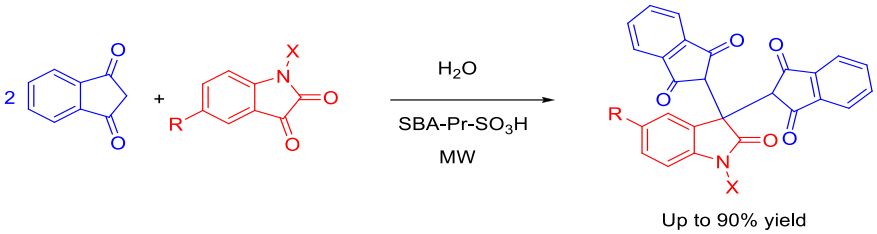
*Bulgarian Chemical Communications, Volume 52, Issue 2 (pp. 184 - 188) 2020* *DOI: 10.34049/bcc.52.2.3977*

# Microwave-assisted synthesis of 2,2′-(2-oxindoline-3,3′-diyl)-*bis*(1*H*-inden-1,3(2*H*)-dione) derivatives using SBA-Pr-$SO_3H$ and their antibacterial activities study

G. Mohammadi Ziarani[1*], Z. Hassanzadeh[1], A. Badiei[2], S. Asadi[1], A. Abolhassani Soorki[3]

[1] *Department of Chemistry, Alzahra University, Vanak Square, Tehran, Iran. gmohammadi@alzahra.ac.ir*
[2] *School of Chemistry, College of Science, University of Tehran, Tehran, Iran*
[3] *ACECR- Research Institute of Applied Sciences, Shahid Beheshti University, Tehran, Iran*

Received July 22, 2015; Revised November 5, 2019




A microwave-assisted protocol for the synthesis of 2,2′-(2-oxindoline-3,3′-diyl)-*bis*(1*H*-inden-1,3(2*H*)-dione) derivatives was reported *via* condensation of isatin derivatives with 1,3-indandione in water as a solvent using SBA-Pr-$SO_3H$ as a nanoporous catalyst. SBA-Pr-$SO_3H$ has the property of being reusable and easily removed from the reaction mixture. Application of SBA-Pr-$SO_3H$ as a nanocatalyst is an efficient strategy for the construction of the oxindole nucleus, because of very short reaction times, good yields and easy work-up. This method is also applicable when isatin is replaced by ninhydrin or acenaphtoquinone compounds.

**Keywords:** Spirooxindole; SBA-Pr-$SO_3H$; Nano catalyst; Microwave irradiation; Multi-component reaction.

## INTRODUCTION

Multi-component reactions (MCRs) have received considerable attention in recent decades due to their atom-economy, flexibility and selectivity. In this method, there is no need to isolate the reaction intermediate, and the time and the raw materials are saved. MCRs are an excellent approach to develop heterocyclic scaffolds to enrich the chemical libraries of drug-like molecules [1-4].

Microwave irradiation as a source of heating shortens the reaction time and has the advantage of being reproducible, offers higher yields and affords an easy scale-up. Association of multi-component reactions and microwave-assisted chemistry effectively diminishes the reaction times and starting material consumption.

The oxindole nucleus has shown a wide range of interesting biological potencies and pharmacological activities such as progesterone receptors agonists, laxative agents, anti-inflammatory, antiprotozoal, antibacterial activities, and it has been used in cancer chemotherapy [5-10]. Isolated oxindoles from marine plants such as bryozoans *Amathia convoluta* showed special activity in the differentiation of Hl-60 human promyelocytic leukemia cells [11].

Mesoporous materials have attracted considerable interest in recent years. These materials showed efficient characteristics including large pore volume, high specific surface area and controllable pore size. These materials were described to have utilization in different fields such as chromatography [12], drug delivery [13], catalysis [14] and adsorption [15]. SBA-15-functionalized sulfonic acid (SBA-Pr-SO3H) as one of the mesoporous materials shows an excellent catalytic property. In continuation of our works on the synthesis of heterocyclic compounds [16-22], SBA-Pr-$SO_3H$ was used as a reusable and highly efficient heterogeneous catalyst. Wide spectrum of biological properties and efficiency of our nanocatalyst brought us to interest in a new approach to develop functionalized oxindoles under microwave irradiation. All above advantages led us to apply microwave irradiation as an efficient source of energy for the SBA-Pr-$SO_3H$-catalyzed one-pot synthesis of 2,2′-(2-oxindoline-3,3′-diyl)bis(1H-inden-1,3(2H)-dione).

* To whom all correspondence should be sent:
E-mail: gmohammadi@alzahra.ac.ir;
gmziarani@hotmail.com

## EXPERIMENTAL

### *Materials and equipment*

All chemicals were purchased from Merck and were used as received. Infrared spectra were recorded from KBr pellets with a FT-IR Bruker Tensor 27 instrument. Mass spectra data were obtained by using Network mass selective detector (Agilent) 6890/5973. Melting points were measured by using a Barnstead Electrothermal 9200 apparatus. $^{1}$HNMR was run on a Bruker DPX, 400 MHz and $^{13}$CNMR on Bruker DPX, 100 MHz in TMS as an internal standard and in DMSO-$d_6$ solvent. A Milestone MicroSYNTH (Microwave Synthesis Labstation) apparatus was used to irradiate the reaction mixture.

### *General procedure for the synthesis of catalyst*

As maintained in our previous report, SBA-15 was synthesized and the interior surface was functionalized with propyl sulfonic acid groups. The result of this functionalization was verified with SEM and TEM images as illustrated in Figure 1. As seen in the SEM image (Figure 1), the morphology of functionalized SBA-15 is the same as of non functionalized SBA-15, which shows that functionalization has not considerably changed its morphology. The TEM image illustrates that during the surface modification of SBA-15, the parallel channels representing the presence of pore configuration of SBA-Pr-$SO_3$H were not collapsed.

### *General procedure for the synthesis of 2,2′-(2-oxindoline-3,3′-diyl)bis(1H-inden-1,3(2H)-dione).*

In this research, condensation of indandione (0.29 g, 2 mmol) **1** and isatin derivatives (1 mmol) **2** was reported in the presence of SBA-Pr-$SO_3$H (0.02 g) as an efficient nanoporous acid catalyst under microwave irradiation (500 W, 95 °C) in water for the synthesis of the oxindole compound. After completion and monitoring of the reaction by TLC, at first, the reaction mixture was filtered, and the crude product was dissolved in hot ethyl acetate in order to remove the SBA-Pr-$SO_3$H nanocatalyst. The pure crystalline product was obtained by cooling the filtrate. As shown in Table 1, the recycled catalyst could be used in subsequent reactions without significant loss of activity.

The physical and spectral (IR, $^{1}$H NMR, $^{13}$C NMR and MS) data for the new compounds are given below:

*2,2′-(5-Chloro-2-oxoindoline-3,3-diyl)bis(1H-indene-1,3(2H)-dione) (**3c**):* Mp = 248-252 °C. IR (KBr): υmax= 3286, 2871, 2675, 1710, 1705, 1614, 1590, 1435, 1256 cm$^{-1}$. $^{1}$H NMR (300 MHz, DMSO-$d_6$) $\delta_H$ (ppm) 4.83 (2H, s, CH), 6.75(1H, d, $^{3}J_{HH}$= 7.5, H-Ar), 7.06 (1H, d, H-Ar), 7.60 (1H, s, H-Ar), 7.93 (8H, bs, H-Ar), 10.77 (1H, s, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_C$ (ppm) 52.2, 53.0, 111.3, 122.8, 125.2, 128.8, 130.2, 136.1, 136.3, 141.8, 141.9, 142.1, 175.5, 196.7, 197.7; MS (*m*/*z*) = 455 ($M^+$), 341, 310, 256, 146, 109, 95, 69 and 43.

*2,2′-(5-Iodo-2-oxoindoline-3,3-diyl)bis(1H-indene-1,3(2H)-dione) (**3e**):* Mp = 268-271 °C. IR (KBr): υmax =3315, 2872, 1707, 1591, 1470, 1262 cm$^{-1}$. $^{1}$H NMR (300 MHz, DMSO-$d_6$) $\delta_H$ (ppm) 4.83 (2H, s, CH), 6.60 (1H, d, $^{3}J_{HH}$= 8.2, H-Ar), 7.0 (1H, s, H-Ar), 7.42 (1H, d, $^{3}J_{HH}$=8.2, H-Ar), 7.94 (8H, bs, H-Ar), 10.77 (1H, s, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_C$ (ppm) 52.0, 53.0, 84.0, 112.3, 122.7, 122.8, 130.8, 131.2, 136.0, 136.3, 137.4, 142.0, 142.1, 142.6, 175.2, 196.8, 197.6; MS (*m*/*z*) = 545 ($M^+$), 401, 290, 190, 146, 118, 107, 90, 76, 63 and 50.

**Table 1**. Synthesis of 2,2′-(2-oxindoline-3,3′-diyl)bis(1H-inden-1,3(2H)-dione) **3a** with recycled SBA-Pr-$SO_3$H.

| | 1st run | 2nd run | 3rd run | 4th run | 5th run |
|---|---|---|---|---|---|
| Time (min) | 3 | 3 | 4 | 5 | 5 |
| Yield* (%) | 90 | 88 | 86 | 85 | 82 |

* Recycle experiments were carried out on reaction of indandione (2 mmol) and isatin (1 mmol) in the presence of SBA-Pr-$SO_3$H, under microwave irradiation. After each run, the regained catalyst can be reactivated by simple subsequent washing with the diluted acid solution, water and acetone.

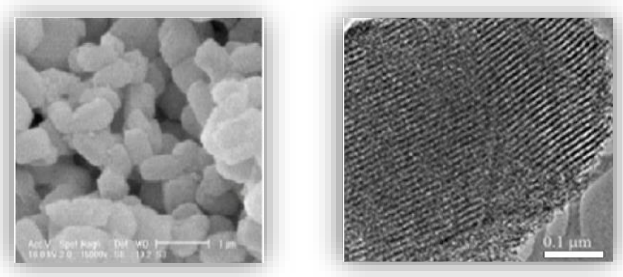



**Figure 1.** SEM image (left) and TEM (right)

## RESULTS AND DISCUSSION

The multi component reaction of indandione (2 mmol) 1 and isatin (1 mmol) 2a was reported using SBA-Pr-$SO_3H$ as an efficient nanoporous acid catalyst under microwave irradiation (500 W, 95 °C) in water for the synthesis of oxindole compound 3a (Scheme 1).

As shown in Table 2, this reaction was extended to various isatin derivatives in the same conditions. In all cases, the products were obtained in a brief reaction time (3 min) with good to excellent yields (75-90 %). To study the generality of this method, isatin was replaced by acenaphthoquinone and ninhydrin molecules, which showed acceptable results (Table 3).

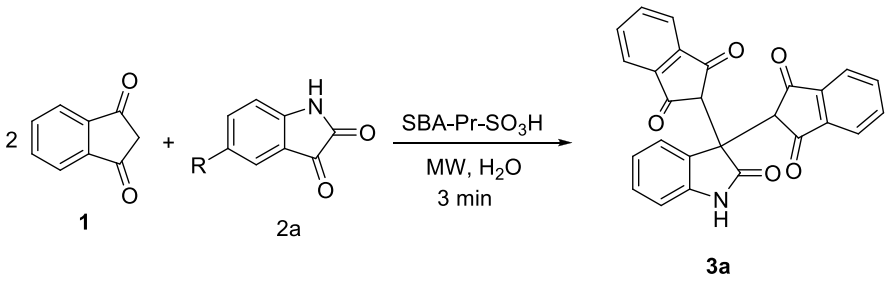
A suggested mechanism for the synthesis of 2,2′-(2-oxindoline-3,3′-diyl)bis(1H-inden-1,3(2H)-dione) derivatives **3** is presented in Scheme 2. At first, a keto-enol tautomerism of indandione **1** is performed in the presence of SBA-Pr-$SO_3H$. Then, a nucleophilic attack of indandione enol form **1** to isatin **2** leads to intermediate **4** which reacts with the second molecule of indandione **1** to give the oxindole compound **3** through dehydration reaction.

To the best of our knowledge, only one case was previously reported in the literature for the synthesis of 2,2′-(2-oxindoline-3,3′-diyl)*bis*(1*H*-inden-1,3(2*H*)-dione) as mentioned in Table 4. The present method has the advantage of accelerating the reaction and leads to good yield of product.

### *Antimicrobial activity*

The antimicrobial activity evaluation of the synthesized compounds was performed through the disk diffusion method (IZ) (Table 5) [23] and the minimum inhibitory concentration technique (MIC) (Table 6) [24]. Their activities were studied against gram positive bacteria *Bacillus subtilis* (ATCC 465) and *Staphylococcus aureus* (ATCC 25923), gram negative bacteria *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 85327) and fungus *Candida albicans* (ATCC 10231).

Compound **5** displays the best results among other compounds against *B. subtilis*, *S. aureus* and *E. coli* with 24, 18 and 10 mm of inhibition zone, respectively. This result was compared to commercial antibiotics such as chloramphenicol, gentamicin and nystatin. Compounds **3b-f** showed poor activity against *B. subtilis* and *S. aureus*. All compounds showed activity against *P. aeruginosa* and *C. albicans*.

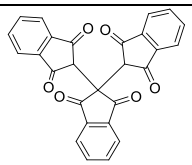
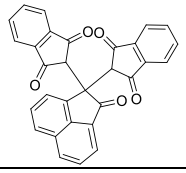


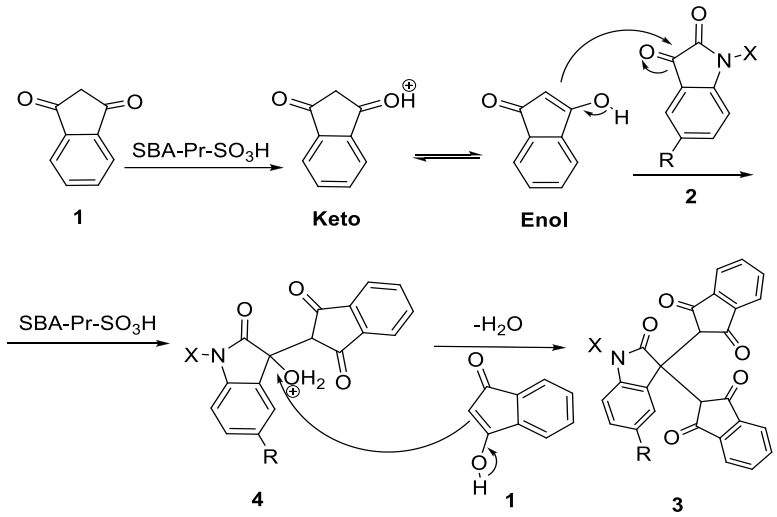

**Scheme 1.** Synthesis of 2,2′-(2-oxindoline-3,3′-diyl)-*bis*(1*H*-inden-1,3(2*H*) dione) **3a** using SBA-Pr-$SO_3H$ under microwave irradiation

**Table 2.** Microwave-assisted synthesis of oxindole derivatives **3** using SBA-Pr-$SO_3H$ in 3 min

| Entry | Product | R | X | Yield (%) | Mp (°C) | Mp [Ref.] |
|---|---|---|---|---|---|---|
| 1 | 3a | H | H | 90 | 256-258 | 255-257 [25] |
| 2 | 3b | Br | H | 84 | 248-250 | 242 [25] |
| 3 | 3c | Cl | H | 80 | 248-252 | New |
| 4 | 3d | $NO_2$ | H | 81 | 240-242 | 234-236 [25] |
| 5 | 3e | I | H | 75 | 268-271 | New |
| 6 | 3f | H | Bn | 84 | 217-220 | 218-221 [25] |

**Table 3.** The results for the replacement of isatin with ninhydrin and acenaphtoquinone

| Entry | Product | Time (min) | Yield (%) | Mp (°C) | Mp [Ref.] |
|---|---|---|---|---|---|
| 1 |  | 3 | 73 | 273 | 276 [25] |
| 2 |  | 6 | 92 | 253 | 240-242 [25] |




**Scheme 2.** Proposed mechanism for the synthesis of 2,2′-(2-oxindoline-3,3′-diyl)bis(1*H*-inden-1,3(2*H*)-dione) derivatives

**Table 4.** Comparison of different conditions in synthesis of 2,2′-(2-oxindoline-3,3′-diyl)*bis*(1*H*-inden-1,3(2*H*)-dione.

| Entry | Catalyst | Solvent | Reaction conditions | Time | Yield **(%)** | Year |
|---|---|---|---|---|---|---|
| 1 | *p*-TSA | EtOH/40 °C | US | 2 h | 81-94 | 2011 [25] |
| 2 | SBA-Pr-$SO_3H$ | $H_2O$ | MW | 3-6 min | 73-92 | Present work |

**Table 5.** Inhibition zone (mm) of the synthesized compounds against some gram positive bacteria, gram negative bacteria and fungi by the disc diffusion method.

| Compound | *B. subtilis* | *S. aureus* | *E. coli* | *P. aeruginosa* | *C.albicans* |
|---|---|---|---|---|---|
| 3a | 0 | 0 | 0 | 0 | 0 |
| 3b | 15 | 16 | 0 | 0 | 0 |
| 3c | 15 | 16 | 0 | 0 | 0 |
| 3d | 15 | 0 | 0 | 0 | 0 |
| 3e | 15 | 16 | 0 | 0 | 0 |
| 3f | 10 | 9 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 |
| 5 | 24 | 18 | 10 | 0 | 0 |
| Chloramphenicol | 26 | 22 | 24 | 8 | - |
| Gentamicin | 28 | 20 | 18 | 18 | - |
| Nystatin | - | - | - | - | 18 |

**Table 6.** Minimum inhibitory concentration (μg/ml) of synthesized compounds against some gram positive bacteria, gram negative bacteria and fungi.

| Compound | *B. subtilis* | *S. aureus* | *E. coli* | *P. aeruginosa* | *C. albicans* |
|---|---|---|---|---|---|
| 3a | - | - | - | - | - |
| 3b | 128 | 64 | - | - | - |
| 3c | 128 | 64 | - | - | - |
| 3d | 128 | - | - | - | - |
| 3e | 128 | 64 | - | - | - |
| 3f | 512 | 512 | - | - | - |
| 4 | - | - | - | - | - |
| 5 | 8 | 64 | 512 | - | - |
| Chloramphenicol | 4 | 8 | 4 | 256 | - |
| Gentamicin | 0.125 | 0.5 | 0.5 | 1 | - |
| Nystatin | - | - | - | - | 8 |

## CONCLUSION

In this work, we have demonstrated an efficient one-pot reaction of isatin with indandione for the synthesis of oxindole derivatives using SBA-Pr-$SO_3H$ as an eco-friendly heterogeneous acid nanocatalyst under microwave irradiation. The advantages of this method are: use of an easily removed catalyst, benign solvent, very fast reaction and high yield. Compounds **3b-f** display antimicrobial activities against some gram positive bacteria, and compound 5 shows the best result among other compounds against *B. subtilis*, *S. aureus* and *E. coli*.

***Acknowledgements:*** *We sincerely acknowledge the financial support provided by the Research Council of Alzahra University, and University of Tehran.*

## REFERENCES

1. D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.*, **44**, 1602 (2005).
2. C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem*., **24**, 4957 (2004).
3. J. Zhu, *Eur. J. Org. Chem.*, **7**, 1133 (2003).
4. J. Zhu, H. Bienaymé, Multicomponent reactions, John Wiley & Sons, 2006.
5. V. V. Bolotov, V. V. Drugovina, S. M. Drogovoz, L.V. Yakovleva, A. I. Bereznyakova, *Pharm. Chem. J.*, **16**, 48 (1982).
6. F. Garrido, J. Ibanez, E. Gonalons, A. Giraldez, *Eur. J. Med. Chem.*, **10**, 143 (1975).
7. H. Pajouhesh, R. Parsons, F.D. Popp, *J. Pharm. Sci* , **72**, 318 (1983).
8. F. D. Popp, *J. Heterocycl. Chem.*, **21**, 1367 (1984).
9. T. Tokunaga, W. E. Hume, J. Nagamine, T. Kawamura, M. Taiji, R. Nagata, *Bioorg. Med. Chem. Lett*., **15**, 1789 (2005).
10. S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton, A. H. White, *Tetrahedron*, **63**, 5579 (2007).
11. Y. Kamano, H.-p. Zhang, Y. Ichihara, H. Kizu, K. Komiyama, G.R. Pettit, *Tetrahedron Lett.*, **36**, 2783 (1995).
12. T. Yasmin, K. Müller, *J. Chromatogr*. A, **1218**, 6464 (2011).
13. S.-W. Song, K. Hidajat, S. Kawi, *Langmuir*, **21**, 9568 (2005).
14. A. Badiei, H. Goldooz, G. Mohammadi Ziarani, *Appl. Surf. Sci.*, **257**, 4912 (2011).
15. T. Tang, Y. Zhao, Y. Xu, D. Wu, J. Xu, F. Deng, *Appl. Surf. Sci.*, **257**, 6004 (2011).
16. G. Mohammadi Ziarani, S. Asadi, A. Badiei, A. Sharifi, M. Amanlou, *Iranian Journal of Pharmaceutical Research*, IJPR, **15**, 55 (2016).
17. G. Mohammadi Ziarani, S. Asadi, A. Badiei, S. Mousavi, P. Gholamzadeh, *Res. Chem. Intermed.*, **41**, 637 (2015).
18. G. Mohammadi Ziarani, S. Faramarzi, S. Asadi, A. Badiei, R. Bazl, M. Amanlou, *DARU*, **21**, 3 (2013).
19. G. Mohammadi Ziarani, M. Rahimifard, F. Nouri, A. Badiei, *J. Serb. Chem. Soc.*, **80**, 1265 (2015).
20. G. Mohammadi Ziarani, A. Badiei, Z. Aslani, N. Lashgari, *Arab. J. Chem.*, **8**, 54 (2015).
21. G. Mohammadi Ziarani, A. Badiei, N. Lashgari, T. Pourjafar, Z. Farahani, *Bulg. Chem. Commun.*, **46**, 719 (2014).
22. G. Mohammadi Ziarani, M.S. Nahad, N. Lashgari, *Bulg. Chem. Commun.*, **47**, 55 (2015).
23. P. NCCLS. Performance Standards for Antimicrobic Disk Susceptibility Tests, National Committee for Clinical Laboratory Standards, Villanova, 1990, Approved Standard M2-A4.
24. w.G.A. NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, 5th edn., NCCLS: Villanova, PA, 2000, Approved Standard M7-A5.
25. R. Ghahremanzadeh, F. Fereshtehnejad, P. Mirzaei, A. Bazgir, *Ultrason. Sonochem.*, **18**, 415 (2011).