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# Nano-cellulose-SBCL5 as a new heterogeneous nano catalyst for the one-pot synthesis of spirooxindoles under mild conditions

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Antimony pentachloride adsorbed on nano cellulose (nano-cellulose-SbCl5) has been found to be a new and highly efficient heterogeneous catalyst for biologically important spirooxindole synthesis under reflux in ethanol. The reaction involves the use of isatins, malononitrile and enolizable systems. A wide range of enolizable systems is compatible in this reaction, producing excellent yields in short time. The morphology of nanocatalyst (nano-cellulose-SbCl5) was observed using a Transmission electron microscopy (TEM). The decomposition steps and thermal stabilitiy of the catalyst were investigeted by thermal analysis techniques (TGA/DTG).

**Key Words**: Spirooxindoles, Isatins, Enolizable system, Nano-cellulose-$SbCl_5$

## INTRODUCTION

Recently, multi-component and domino reactions are efficient and effective methods in the sustainable synthesis of heterocycles. Due to atom economy and simplicity of one-pot procedures, multi-component reactions occupy a superior position compared with other reactions. These reactions are widely applied in pharmaceutical chemistry for producing different structures and combinatorial libraries for drug discovery [1-3]. The spirooxindole derivatives are included in numerous natural products and they are dominant molecules in medicinal chemistry, such as pteropodine, horsfiline, isopteropodine and spirotryprostatin A, B [4]. On the basis of biological studies, the existence of two different heterocyclic moieties in a single molecule often show enhances the biological activity dramatically [5-7].

One of the protocols for the construction of spirooxindole derivatives is condensation of an isatin, malononitrile and enolizable systems in the presence of an acidic nano catalyst. Previously, $InCl_3$ [8], Triethylbenzylammonium chloride [9], Sodium stearate [10], $I_2$ [11], silica sulfuric acid nanoparticles [12], $HAuCl_4.3H_2O$ [13] and $NH_4Cl$ [14] were applied for this method as catalyst.

Solid supported reagents have improved activity and selectivity than individual reagents [15]. We have been engaged recently in developing heterogeneous catalysts derived from silica and nano silica-supported protic and Leiws acids for various organic transformations [16-20]. In this investigation, we present nano-cellulose-$SbCl_5$ as a new, highly efficient and heterogeneous catalyst for the synthesis of spirooxindole derivatives.

## EXPERIMENTAL

All of compounds were analytical grade reagents and were used as received, without any further purification. The chemicals for this work were purchased from Fluka. Melting points were determined with an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. The NMR spectra were obtained on a Bruker Avance DRX-400 FT spectrometer ($^1$H NMR at 400 Hz, $^{13}$C NMR at 100 Hz) using DMSO-$d_6$ as solvent with TMS as internal standard. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Science and Research Unite of Islamic Azad University. The morphologies of the nano composite were observed using TEM of Philips CM120. Thermogravimetric analysis was performed by using a TG of Netzsch STA 409 PC.

The stable nano-cellulose is prepared [21,22] and used for preparation of catalyst (nano-cellulose-$SbCl_5$).

### *Synthesis of antimony pentachloride adsorbed on nano cellulose (nano-cellulose-$SbCl_5$)*

To a stirred mixture of nano-cellulose (1g) and diethyl ether (15 ml), antimony pentachloride (1 ml) was added dropwise at 0 °C during 15 min. The reaction mixture was filtered, washed well with diethyl ether and dried at room temperature.

### *General procedure for the preparation of compounds 4a-l*

Nano-cellulose-$SbCl_5$ (0.006 g) was added to a stirred mixture of the isatins (1 mmol, 1a-c), enolizable system (1 mmol) and malononitrile (1.2 mmol) in EtOH (5 mL). The materials were mixed

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and refluxed for the 15 min. The progress of the reaction was followed by TLC (*n*-hexane: ethyl acetate, 3:1). After completion of the reaction, the mixture was filtered to remove the catalyst. After evaporation of the solvent, the crude product was re crystallized from hot ethanol to obtain the pure compound.

Spectral data for selected compounds:

*2-Amino-5,7-dioxo-spiro[(3′H)-5′-Fluoro-indol-3′,4,4(H)-5,6,7,8-tetrahydropyrano (2,3-d)pyrimidine]-(1′H)-2′- one-3-carbonitrile (**4g**)*

White solid; mp 246-248ºC; IR (KBr) $\nu_{max}$ 3395, 3385, 3160, 2200,1716, 1692, 1671, 1483, 1390, 1223, 1108, 796 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ 12.31 (s, 1H, NH), 11.14 (s, 1H, NH), 10.49 (s, 1H, NH), 7.42 (s, 2H, $NH_2$), 7.15 (dd, 1H, *J*=8.2 Hz, *J*=2.6 Hz, ArH), 6.96 (dd, 1H, *J*=2.6 Hz, *J*=1.0 Hz, ArH), 6.77 (d, 1H, *J*=4.3Hz, ArH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100MHz) δ 178.1, 161.9, 159.9, 158.8, 157.5, 153.9, 149.7, 138.7, 135.8, 117.2, 115.1, 112.3, 110.3, 86.8, 56.9 ppm. Anal. Calcd. For $C_{15}H_8FN_5O_4$: C, 52.81; H, 2.34; N, 20.52 Found: C, 52.76; H, 2.22; N, 20.46%.

*2-Amino-5-oxo-7-thioxo-spiro[(3′H)-5′-nitro-indol-3′,4,4(H)-5,6,7,8-tetrahydropyrano(2,3-d)pyrimidine]-(1′H)-2′-one-3-carbonitrile (**4k**)*

Cream, Solid; mp 268-270 ºC; IR (KBr) $\nu_{max}$ 3495, 3135, 3025, 2860, 2195, 1709, 1580, 1343, 1132, 835 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 11.29 (s, 2H), 8.35 (d, *J*=2.4Hz, 1H), 8.18 (dd, *J*=8.6 Hz, *J*=2.4Hz, 1H), 7.62 (s, 2H), 7.03 (d, *J*=8.6 Hz, 1H) ppm; $^{13}C$ NMR (101 MHz, DMSO) δ 177.9, 174.0, 162.9, 159.3, 158.4, 153.2, 148.5, 142.6, 134.0, 126.0, 120.3, 116.5, 109.4, 90.5, 55.9, 46.7 ppm. Anal. Calcd. For $C_{15}H_8N_6O_5S$: C, 46.87; H, 2.09; N, 21.86 Found: C, 46.84; H, 2.11; N, 21.83%.

*2-Amino-5-oxo-spiro[4,5,6,7,8-tetrahydrocyclopenta(b)pyran -4,3′-(3′H)-5′-nitro-indol]-(1′H)-2′-one-3-carbonitrile (**4l**)*

Red Solid; mp 293-295 ºC; IR (KBr) $\nu_{max}$ 3450, 3300, 3195, 3020, 2185, 1739, 1506, 1339, 1103, 833 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400MHz) δ 11.33 (s, 1H, NH), 8.29 (s, 1H, ArH), 8.18 (s, 1H, ArH), 7.70 (s, 2H, $NH_2$), 7.05 (s, 1H, ArH), 2.81 (s, 2H, $CH_2$), 2.47 (s, 1H, $CH_2$), 2.36 (s, 1H, $CH_2$) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100MHz) δ 201.0, 179.2, 178.1, 161.4, 148.7, 143.2, 133.3, 126.8, 120.6, 117.7, 113.9, 110.4, 55.4, 47.1, 33.6, 25.6 ppm. Anal. Calcd. For $C_{16}H_{10}N_4O_5$: C, 56.80; H, 2.97; N, 16.56 Found: C, 56.75; H, 2.90; N, 16.52%.

*2-Amino-5,7-dioxo-spiro[(3′H)-5′-nitro-indol-3′,4,4(H)-5,6,7,8-tetrahydropyrano(2,3-d)pyrimidine]-(1′H)-2′-one-3-carbonitrile (**4m**)*

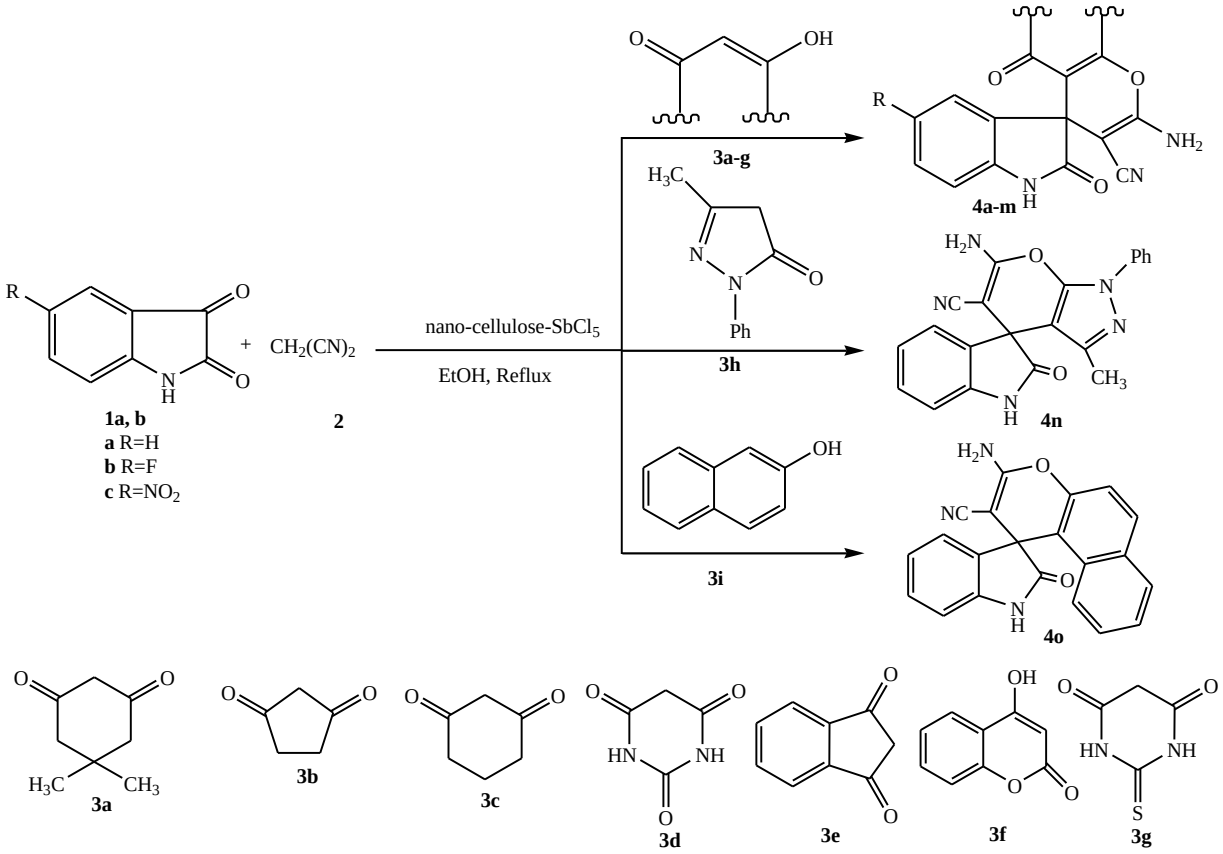
Light cream, Solid; mp 380-385 ºC; IR (KBr) $\nu_{max}$ 3400, 3295, 3180, 2820, 2195, 1745, 1694, 1519, 1390, 1120, 833 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400MHz) δ 12.40 (s, 1H, NH), 11.22 (s, 1H, NH), 11.18 (s, 1H, NH), 8.24 (s, 1H, ArH), 8.14 (d, 1H, *J*=8.8 Hz, ArH), 7.56 (s, 2H, $NH_2$), 6.99 (d, 1H, *J*=8.4Hz, ArH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100MHz) δ 178.0, 163.2, 160.2, 155.5, 150.8, 150.2, 144.1, 136.2, 127.5, 121.6, 118.3, 111.0, 57.7, 48.4 ppm. Anal. Calcd. For $C_{15}H_8N_6O_6$: C, 48.92; H, 2.18; N, 22.82 Found: C, 48.90; H, 2.19; N, 22.76%.

## RESULTS AND DISCUSSION

In continuation of our investigation about application of nano solid acids in organic synthesis, we investigated the synthesis of spirooxindoles in the presence of nano-cellulose-$SbCl_5$ as an inorganic polymeric solid acid. The catalytic activity of nanocatalyst was investigated for synthesis of spirooxindole derivatives, by the condensation of an isatin **1**, malononitrile **2** and enolizable system **3** (Scheme 1).

The morphology and size of nanoparticles was observed by TEM images. As shown in Figure 1, the size of nano-cellulose-$SbCl_5$ is below 100 nm.

The thermal decomposition of nano-cellulose-$SbCl_5$ catalysis was examined, using a combination of thermogravimetry (TGA) and derivative thermogravimetry (DTG) under nitrogen atmosphere over 800˚C. The structural conversion was observed by TG curves. They were supported by the obtained DTG data. Thermal analysis was found being useful structural elucidation nano-cellulose-$SbCl_5$. The thermal stability and also the decomposition mode were carefully controlled under heating rate. In fact, two thermal decomposition mass loss steps were realized for the nano-cellulose-$SbCl_5$ catalysis (Fig. 2). The catalyst is stable up to 200°C, after it, the first stage ofdegradation up to 500 °C and 64.37%, DTG curve exhibits mass losses, most probably due to the common degradation of the cellulose units. The mass loss of 32.52% at the second stage can be well attributed to the DTG peak of 500 to 700 °C, it is a common mass for decomposition of lignin.




**Scheme 1.** Synthesis of spirooxindole derivatives in the presence of nano-cellulose-$SbCl_5$ as catalyst

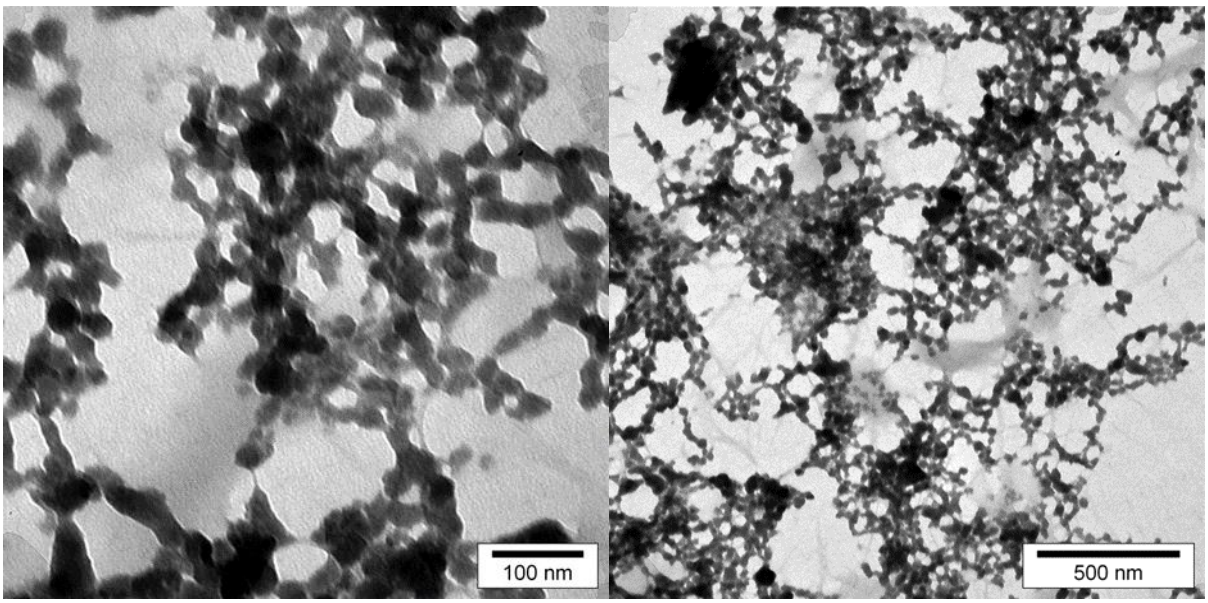



**Fig. 1**. TEM micrographs of nano-cellulose-$SbCl_5$

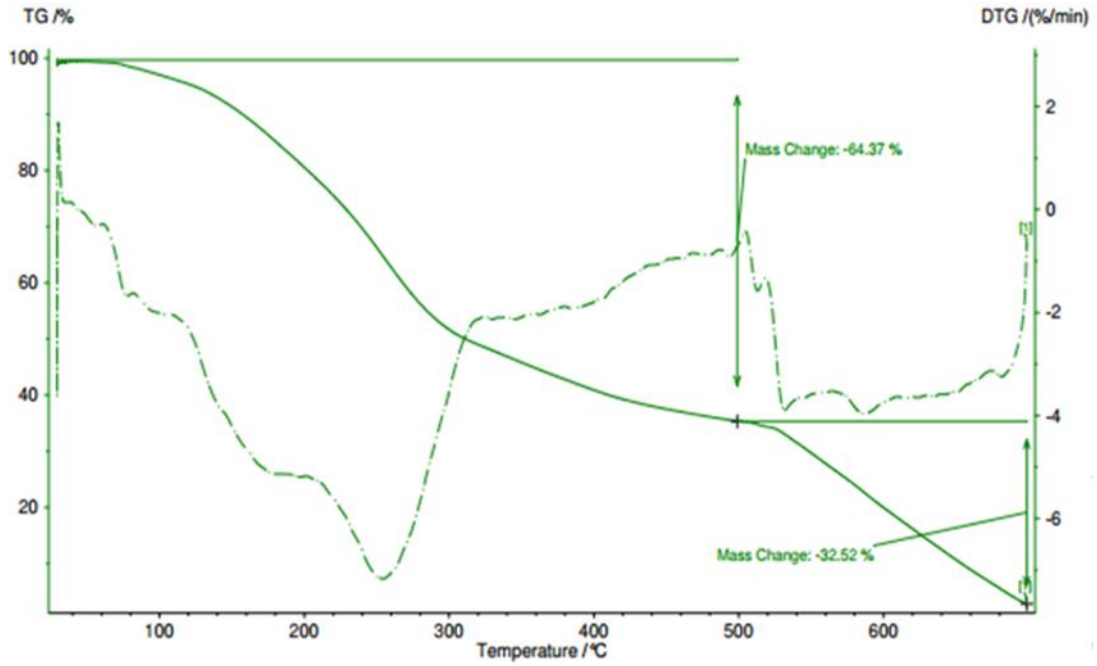



**Fig. 2**. The TGA/DTG curves of nano-cellulose-$SbCl_5$

To optimize the reaction conditions, the reaction of isatin, dimedone and malononitrile was used as a model reaction. In order to establish better catalytic activity of nano-cellulose-$SbCl_5$, the model reaction was compared with other catalysts reported in literature. As shown in Table 1, the condensation of isatin with malononitrile and dimedone catalyzed by nano-cellulose-$SbCl_5$ in EtOH offers production of the corresponding product **4a** in shorter time, much efficient yield and milder condition is done, while other methods require more amount of catalyst and longer reaction time (Table 1, entries 1-6) for synthesis of spirooxindole **4a**.

**Table 1.** Optimization of the reaction conditions for synthesis of **4a**

| Entry | Catalyst (amount) | Solvent/Condition | Time(min) | Yield[Ref.] |
|---|---|---|---|---|
| 1 | $InCl_3$ (20 mol%) | $CH_3CN$/reflux | 90 | 75[6] |
| 2 | TEBA[a] (20 mol%) | $H_2O$/60ºC | 120 | 94[7] |
| 3 | Sodium stearate (10 mol%) | $H_2O$/60ºC | 180 | 95[8] |
| 4 | $I_2$ (10 mol%) | $H_2O$/50ºC | 60 | 80[9] |
| 5 | $HAuCl_4.3H_2O$ (5 mol%) | PEG[b] 400/70 ºC | 30 | 96[10] |
| 6 | $NH_4Cl$ (20 mol%) | $H_2O$/80 ºC | 10 | 92[11] |
| 7 | $SiO_2$-$OSO_3H$ NPs (0.003g) | EtOH/reflux | 20 | 96[12] |
| 8 | Nano $SiO_2$ (0.04g) | EtOH/reflux | 15 | 72 |
| 9 | Nano-cellulose-$SbCl_5$ (0.004g) | EtOH/reflux | 15 | 82 |
| 10 | Nano-cellulose-$SbCl_5$ (0.006g) | EtOH/reflux | 15 | 96 |
| 11 | Nano-cellulose-$SbCl_5$ (0.008g) | EtOH/reflux | 15 | 97 |
| 12 | Nano-cellulose-$SbCl_5$ (0.006g) | $CH_2Cl_2$/reflux | 15 | 65 |
| 13 | Nano-cellulose-$SbCl_5$ (0.006g) | $H_2O$/reflux | 15 | 85 |
| 14 | Nano-cellulose-$SbCl_5$ (0.006g) | $CH_3CN$/reflux | 15 | 47 |
| 15 | Nano-cellulose-$SbCl_5$ (0.006g) | Solvent-free[c] | 15 | 58 |
| 16 | Nano-cellulose-$SbCl_5$ (0.006g) 2nd run | EtOH/reflux | 15 | 89 |
| 17 | Nano-cellulose-$SbCl_5$ (0.006g) 3rd run | EtOH/reflux | 15 | 82 |

[a] Triethylbenzylammonium chloride; [b] Polyethylene glycol; [c] 15 min at 70 °C

In order to determine the optimum quantity of nano-cellulose-$SbCl_5$, the reaction of isatin, dimedone and malononitrile was carried out under reflux in ethanol using different quantities of nano-cellulose-$SbCl_5$ (Table 1, entries 8-10). As shown in Table 1, 0.006 g of nano-cellulose-$SbCl_5$ gives an excellent yield in 15 min.

The above reaction was also examined in various solvents at reflux temperature (Table 1, entries 9, 11-13). The results indicated that different solvents affected the efficiency of the reaction. Most of these solvents required a longer time and give moderate yields. The best results were obtained when EtOH was used. An interesting

feature of this approach is that the catalyst can be regenerated at the end of the reaction and can be used multiple times without losing its activity. To recover the catalyst, after completion of the reaction, the mixture was filtered and recrystallized from hot ethanol; catalyst was separated and washed with $CHCl_3$ and then dries the solid residue. This process repeated for two cycles and the yield of product **4a** did not change significantly (Table1, entry 15, 16).

To study the scope of the reaction, a series of enolizable systems and isatin with malononitrile were examined by nano-cellulose-$SbCl_5$ as catalyst. The results are shown in Table 2. In all cases, enolizable systems with C-H acid groups underwent the reaction smoothly and formed products in approving yields. For further investigation, the reaction of 5-Fluoroisatin and 5-Nitroisatin was also studied. 5-Fluoroisatin and 5-Nitroisatin reacted with enolizable system such as dimedone, cyclohexadione, cyclopentadione, 1, 3-indandione, barbituric acid and thiobarbituric acid with malononitrile under optimized reaction conditions, and products **4f-m** were produced with good to excellent yields (Table 2, entries 6-13).

**Table 2.** Condensation of isatins, enolizable system and malononitrile in the presence of nano-cellulose-$SbCl_5$ catalyst

| Entry | R | Enolizable system | Product | Yield(%)[a] | m.p.(ºC) found | m.p.(ºC) Reported[6-12] |
|---|---|---|---|---|---|---|
| 1 | H | 3a | 4a | 96 | 265-267 | 268 |
| 2 | H | 3b | 4b | 92 | >300 | >300 |
| 3 | H | 3c | 4c | 93 | >300 | >300 |
| 4 | H | 3d | 4d | 88 | 274-276 | 275-276 |
| 5 | H | 3f | 4e | 88 | 292-295 | 292-294 |
| 6 | F | 3a | 4f | 93 | 270-272 | 270-273 |
| 7 | F | 3d | 4g | 92 | 246-248 | - |
| 8 | F | 3b | 4h | 90 | >300 | 313-316 |
| 9 | F | 3c | 4i | 90 | 290-292 | 289-291 |
| 10 | F | 3e | 4j | 89 | 286-288 | 286-288 |
| 11 | $NO_2$ | 3g | 4k | 89 | 268-270 | - |
| 12 | $NO_2$ | 3b | 4l | 94 | 293-295 | - |
| 13 | $NO_2$ | 3d | 4m | 92 | >300 | - |
| 14 | H | 3h | 4n | 85 | 238-239 | 236-237 |
| 15 | H | 3i | 4o | 83 | 234-236 | 236 |

[a] Yields refer to pure isolated products

## CONCLUSIONS

In conclusion, we have developed a simple and facile heterogeneous catalytic procedure for the preparation of spirooxindoles via cyclocondensation of isatins with malononitrile and enolizable systems in the presence nano-cellulose-$SbCl_5$ under reflux in ethanol. Straightforward operation, non-toxicity, low cost, short reaction times, high yields and simple work-up are the key features of this method which make it an attractive to the procedures reported in the literature. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

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## REFERENCES

1. Armstrong, R. W. Combs, A. P. Tempest, P. A. Brown, S. D. Keating, T. A. Acc. *Chem. Res*. **29**, 123(1996)
2. Dax, S. L. McNally, J. J. Youngman, M. A. Curr. Med. *Chem*. 6, 255 (1999 .(
3. Braun, R. Zeitter, K. Müller, T. Org. Lett. **3**, 3297 (2001)
4. Kang, T.-H. Matsumoto, K. Murakami, Y. Takayama, H. Kitajima, M. Aimi, N. Watanabe, H. Eur. J. Pharmacol. **444**, 39 (2002)
5. Ballini, R. Bosica, G. Conforti, M. L. Maggi, R. Mazzacanni, A. Righi, P. Sartori, G. Tetrahedron, **57**, 1395 (2001)
6. Elagamay, A. G. A. El-Taweel, F. M. A. A. Indian J. *Chem. Sec. B*, **29**, 885 (1990)
7. Hiramoto, K. Nasuhara, A. Michiloshi, K. Kato, T. Kikugawa, K. Mutat. Res. **395**, 47 (1997)
8. Shanthi, G. Subbulakshmi, G. Perumal, P.T. Tetrahedron, **63**, 2057 (2007)
9. Zhu, S-L. Ji, S-J. Zhang, Y. Tetrahedron, **63**, 9365 (2007)
10. Wang, L-M. Jiao, N. Qiu, J. Yu, J-J. Liu, J-Q. Guo, F-L. Liu, Y. Tetrahedron, **66**, 339 (2010)

11. Kidwai, M. Jain, A. Nemaysh, V. Kumar, R. Luthra, P M. Med. Chem. Res. **22**, 2717 (2013)
12. Sadeghi, B. Ghasemi pirbaluti, M. Farokhi nezhad, P. Abbasi nezhad, R. Res. Chem. Intermed.**41**, 4047 (2015)
13. M. Kidwai, A. Jahan, N.K.. Mishra, *Appl. Catal. A: Gen*. **425-426**, 35 (2012)
14. Dabiri, M. Bahramnejad, M. Baghbanzadeh, M. Tetrahedron, **65**, 9443 (2009)
15. Corma, A. Garcia, H. Adv. Synth. Catal. **348**, 1391 (2006)
16. Mirjalili, B. F. Hashemi, M. M. Sadeghi, B. Emtiazi, H. J. Chin. *Chem. Soc*. **56**, 386 (2009)
17. Sadeghi, B. Mirjalili, B. F. Bidaki, S. Ghasemkhani, M. J. Iran. *Chem. Soc*., **8**, 648 (2011)
18. Sadeghi, B. J. Chem. Res. 37, 171 (2013)
19. Sadeghi, B. FarokhiNezhad, P. Hashemian, S. J. *Chem. Res*. **38**, 54 (2014)
20. Sadeghi, B. Scientia Iranica C, **21**, 708 (2014.(
21. Mirjalili, B. F. Bamoniri, A. Mirhoseini, M.A. *Scientia Iranica C*, **20**, 587 (2013)
22. Maiti, S. Jayaramudu, J. Das, K. Reddy, S. M. Sadiku, R. Ray, S. S. Liu. D.Carbohydr. Polym. **98**, 562 (2013).