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Synthesis of 3, 3-Di Indolin-2-One's in Presence of Zro_2/Sba-15 as an Efficient, Reusable Nano Catalyst

Bhavani Atyam[1]*, Annpurna Nowduri[1], Srividya Maripi[1] and Ch. Sanuradha[2]

1. Department of Engineering Chemistry, A.U. College of Engineering (A), Andhra University, Visakhapatnam – 530 003, Andhra Pradesh, **INDIA**
2. Department of Chemistry, Visakhapatnam Government Degree College for Women, Visakhapatnam, Andhra Pradesh, **INDIA**

Email:bhavanichematyam@gmail.com

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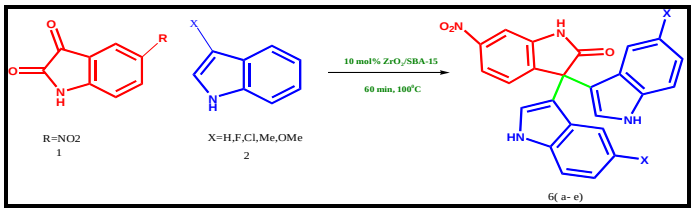
ABSTRACT

A simple and an efficient, multi component, one pot synthesis has been developed for the synthesis of 3,3-di indolin-2-one's and their derivatives by using reusable, easily separable ZrO_2/SBA-15 nano catalyst. The reaction, with these catalyst was carried out under mild and eco friendly conditions, with good yields of 3,3-di indolin-2-one's. The synthesized 3,3-di indolin-2-one's and their derivatives are characterized by ^1H NMR, ^{13}C NMR and Mass spectroscopy.

Graphical Abstract



Model reaction

Keywords: 3,3-di indolin-2-one's, ZrO_2/SBA-15 as an efficient catalyst.

INTRODUCTION

Multicomponent reaction plays a major role in organic synthesis. The main advantages of MCRs shorten the reaction time, minimize the byproducts, the most of the multi component reactions proceeds through convergent reaction way in which three or more starting materials in single reactant to form without any intermediates [**1, 2**]. And also these multi component reactions have broad range applications in heterocyclic compound synthesis and combinational synthesis [**3-6**]. Isatine is the major molecule in the designing of bio active agents they are anti fungal [**7**], anti HIV [**8**], anti tumor [**9**], anti viral [**10**] and anti convulsants [**11**]. Indoles and their derivatives found in nature they exhibit physiochemical properties [**12-14**]. In certain, 3,3-diaryloxindole is normally found in biologically

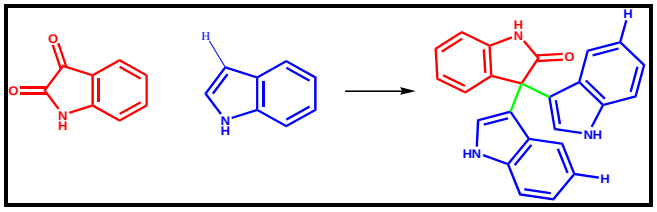
active compounds and also clinical drugs. Predominantly, bis indole methanes segregate from natural sources like vibrindole. 3,3-di (indolyl) indolin-2-one also called as bis indoles are prepared by coupling of isatin with indoles under acidic conditions [**15-16**]. B. V Reddy et al synthesize the bis indoles by using iodine catalyst [**17**]. Although, some methodologies' might have been described synthesis of 3, 3-di (indolyl) indolin-2-ones [**18-23**]. Accordingly the development of elementary and an efficient method reported for the synthesis of [3, 3':3', 3"-terindolin]-2'-one derivatives.

Herein, in order to achieve a more efficient synthetic process, minimize by-products, decrease the number of separate reaction steps, improving the yields and reaction times and also in extending our research on the application of nanocatalyst in MCRs, in this we report a clean and environmentally friendly approach to the synthesis of [3, 3':3', 3"-terindolin]-2'-one derivatives, via multi-component reaction in the presence of silica coated zerconia nano catalyst (ZrO2/SBA-15). SBA-15 mesoporous silica was prepared according to literature described elsewhere [**24-29**]. ZrO2/SBA-15 catalyst was prepared by wet impregnation method with zirconium acetyl acetonate as zirconia precursor and SBA-15 [**30**].

MATERIALS AND METHODS

Entire reagents and chemicals were adequate from Sigma- Aldrich St. Louis, MO, USA), Lancaster (Alfa Aeser, Johnson Matthey Company, Ward Hill, MA, USA), or Spectrochem Pvt. Ltd. (Mumbai, India) and were used an absence of any further purification tests. Progress of each reaction was examined by TLC on silica gel glass plate containing GF-254, and visualization was accomplished with UV lamp of 12 stains. All the products were characterized by their NMR and Mass spectra. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz and 75 MHz, in CDCl3/DMSO, and the chemical shifts were reported in parts per million (ppm, δ) downfield from the Tetramethyl silane (TMS)

General Experimental Procedure For Synthesis 3,3-Di Indolin-2-One's: In this reaction isatin (1 mmol), indole (2 mmol), 10 mol% ZrO_2/SBA-15 and water as solvent were taken in a 100 ml round bottom flask. The reaction mixture was agitated for 2 h, at 100°C. The progress of the reaction was observed by TLC. After the accomplishment of the reaction the catalyst was isolated by using simple filtration and cooled the reaction mixture was filtered and the obtained solid product is cleanse with ethyl acetate before drying over Na_2SO_4. After transferring the solvent in vacuous, the rest of the part was purified by silica-gel chromatography to give the requisite 3,3-di indolin-2-one's in excellent yields. The identity and purity of the products were confirmed by 1H, 13C NMR, and mass spectra.



Scheme 1 General Reaction.

RESULTS AND DISCUSSION

Synthesis of 3,3-di indolin-2-one's, we began our investigations by screening the reaction of isatine and indole were taken in different solvents (Ethanol, CH_3CN, DMSO, Water) in absence of ZrO_2/ SBA-15 catalyst and results were captured in table.1. It was clearly observed that low yield of products were obtained with ethanol, CH_3CN, DMSO, (Table1, entry 1-5) respectively even after 4 h stirring. From table 1, it is evident that low product yields. There was a slight increase in yield (Table 1, entry 6-10), when the reaction mixture was added with 5 mol% ZrO_2/SBA-15 catalyst even on stirring for just 2 h at 50°C. It was observed that yield (46%) obtained was much better in water as

solvent at the same reaction conditions. On increasing the catalyst to 10 mol%, the yield increased up to 97% respectively at 100°C. (Table 1 entry 10). All the results were summarized in table 1. No change was observed on further enhancing the catalyst mol% or time of stirring. The model reaction may be summarized as follows 3,3-di indolin-2-one'ssynthesized by reacting isatine and indole using 10 mol% ZrO_2/SBA-15 catalyst in water and obtained 97% yields at 100°C. Continuing the success, different isatines and were tested in our attempt to synthesis 3,3-di indolin-2-one's derivatives at the same reaction conditions and the results are summarized in table 2. From the results as is evident from table 2, we can conclude that the indols with strong electron releasing groups such gave excellent yields. (Table 2) 3d, 3e, 6d and 6e are formed in 94-97% yields. Indoles with weak electron releasing groups also gave good yield, but less than former case (Table 2) 3a, 3b, 3c, 6a, 6b and 6c. The structures of synthesized 3,3-di indolin-2-one's are confirmed by ^{1}HNMR, ^{13}CNMR and Mass spectra analysis.

Table 1. Optimization of synthesis of 3,3-di indolin-2-one'sin presence of ZrO_2/SBA-15 as a catalyst in different solvents

S.No	Solvent	Catalyst (mol%)	Time (h)	Temp. (°C)	Yield (%)
1	-	-	4	RT	-
2	Ethanol	-	4	RT	10
3	CH_3CN	-	4	RT	10
4	DMSO	-	4	RT	10
5	Water	-	4	RT	10
6	Ethanol	5	2	50	16
7	CH_3CN	5	2	50	21
8	DMSO	5	2	50	23
9	Water	5	2	50	46
10	Water	10	2	100	97
11	Water	15	2	100	97
12	Water	20	2	100	97

The plausible mechanism for the formation of 3,3-di indolin-2-one'sfrom 6- chloroindoline-2,3-dione and 1H-indole using ZrO_2/SBA-15 is shown in figure 1. The reaction may proceed through the formation of highly reactive (Z)-6-chloro 3-(3H-indol-3-ylidene) indolin-2-one. The efforts to isolate intermediates were not successful.

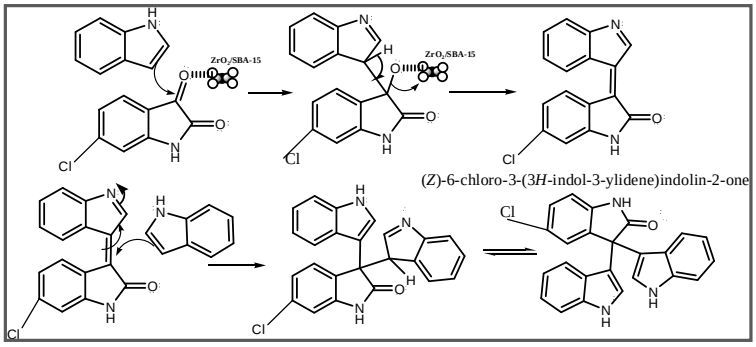
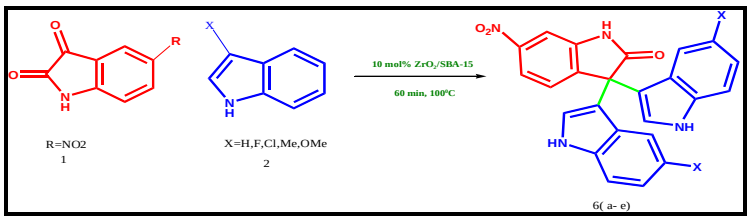
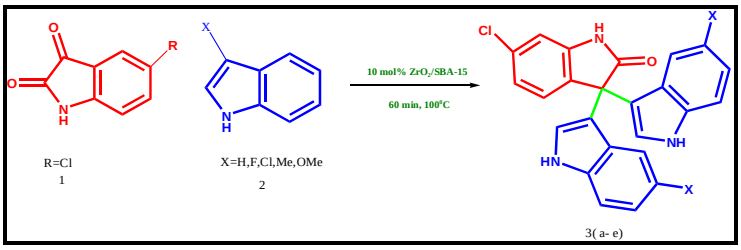


Figure 1. Plausible Mechanism



Scheme 2. Model reaction.



Scheme 3. Model reaction.

Reusability of the catalyst: The reusability of ZrO_2/SBA-15 is one of the most important advantages of this protocol that makes it useful for practical commercial applications. We have investigated the reusability of ZrO_2/SBA-15 catalyst for the model reaction. Interestingly, the retained catalyst could be reused for up to five cycles which is evident from table 3. The catalyst was isolated by using simple filtration after a completion of the reaction, cleansed with water followed by chloroform, dried in oven and reused for the next cycle.

Table 3. Productivity with re-cycle catalyst

Entry	Catalyst	Yield
1	1st cycle	94
2	2nd cycle	92
3	3rd cycle	90
4	4th cycle	87
5	5th cycle	85

Spectral analysis data of synthesized compounds

3a) 6-Chloro-3,3-di(1h-indol-3-yl)indolin-2-one: White Solid; Mp: 332-335°C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.06-7.32(7H,m), 7.40–7.47 (2H,m), 7.54–7.62(4H, q J= 8.120), 10.69(1H, s), 10.82 (2H,s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.5; 109.9; 111.8; 112.9; 113.9; 121.8; 122.9; 123.9; 124.8; 125.7; 127.2; 127.8; 133.6; 135.6; 140.6; 179.2. ESI-MS: m/z = 397.86 $(M+H)^+$.

3b) 6-chloro-3,3-bis(5-fluoro-H-indol-3-yl)indolin-2-one: White solid; Mp: 298-300°C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.9-7.02(2H, d t, J_1= 2.26, J_2 = 6.79) 7.11-7.22(5H,m), 7.38-7.49(4H,m), 7.80(1H,s), 10.39(1H,s), 10.62(2H,s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.7; 109.1; 111.9; 113.3; 119.2; 120.5; 120.9; 122.9; 124.0; 125.0; 125.5; 127.1; 133.0; 134.7; 140.3; 178.3. ESI-MS: m/z = 433.08 $(M+H)^+$.

3c) 6-chloro-3,3-bis(5-chloro-H-indol-3-yl)indolin-2-one: Light brown solid; Mp: >350°C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.13-7.24 (6H,m), 7.39-7.53(5H,m) 10.35(1H,s), 10.61(2H,s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.3; 104.1; 104.4; 108.0; 108.3; 108.7; 111.0; 111.1; 113.2; 120.4; 123.6; 124.7; 125.0; 126.7; 132.5; 132.9; 140.1; 153.8; 156.9; 177.8. ESI-MS: m/z = 466.75 $(M+H)^+$.

3d) 6-chloro-3,3-bis(5-methyl-H-indol-3-yl)indolin-2-one: Pale pink solid; Mp: 335-337°C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23(3H,s) 2.37(3H,s) 6.85-6.91(2H,m) 7.01-7.20(5H,m) 7.37-7.47(4H,m), 10.18-1.24(3H,s,brs). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.2; 108.0; 108.8; 109.1; 116.5; 119.7; 118.2; 124.1; 125.8; 126.4; 130.6; 132.6; 133.6; 134.2; 139.7; 178.3. ESI-MS: m/z = 425.91 $(M+H)^+$.

3e) 6-chloro-3,3-bis(5-methoxy-H-indol-3-yl)indolin-2-one: Light yellow solid; Mp: >350°C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79(6H,s), 6.91-7.01(4H,m), 7.11-7.21(4H,m) 7.37–7.53 (3H,m) 9.78(2H,s) 10.01(1H,s). ^{13}C NMR (75 MHz, DMSO-d_6): 52.1; 54.6; 102.6; 108.8; 110.0; 111.1; 113.1; 120.7; 124.2; 124.5; 125.5; 126.8; 131.5; 133.9; 140.5; 151.9; 178.7. ESI-MS: m/z = 457.91$(M+H)^+$.

6a) 3,3-di(1H-indo1-3-yl)-6-nitroindolin-2-one: Pale pink solid; Mp: 325-327°C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.8-7.08(7H,m), 7.17-7.40(6H,m), 10.46(1H,s), 10.58(2H,s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.5; 109.3; 110.0; 112.1; 116.8; 119.1; 119.4; 122.8; 123.2; 124.0; 124.4; 125.9; 134.9; 135.5; 138.5; 177.2. ESI-MS: m/z = 408.41 $(M+H)^+$.

6b) 3,3bis(5-floro-1H-indol-3-yl)6-nitroindolin-2-one: White color solid. ;Mp: >350°C:^{1}H NMR (300 MHz, DMSO-d_6): δ 6.79-6.86 (2H,dt J_1= 2.26, J_2 = 6.79)) 6.94-7.02(5H,m) 7.15-7.23(2H,m), 7.31-7.36(2H,q J= 8.120), 10.52(1H,s), 10.75 (1H,s).^{13}CNMR (75MHz,DMSOd_6): δ51.93, 124.87, 124.48,110.42,109.72,112.57,119.91,117.28,123.71,126.54,135.99,135.41,138.98,177.70. ESI-MS: m/z = 444.39 $(M+H)^+$.

6c) 3,3bis(5-chloro-1H-indol-3-yl)6-nitroindolin-2-one: Grey color solid; Mp: 250-252°C:^{1}H NMR (300 MHz, DMSO-d_6): δ 6.93(2H,d), 7.00-7.50(2H ,d, J=8.120), 7.13(1H,s), 7.21- 7.24(1H, d J= 2.26) 7.33-7.36(4H,d J= 6.79), 7.66(1H,s), 10.48(1H,s), 10.78(2H,s).^{13}C NMR (75 MHz, DMSO-d_6): δ 50.8; 103.6; 103.9; 107.5; 107.8; 108.2; 110.6; 112.7; 119.9; 123.1; 124.2; 124.5; 126.2; 132.0; 132.4; 139.6; 153.3; 156.4; 177.3. ESI-MS: m/z = 477.30 $(M+H)^+$.

6d) 3,3bis(5-mrthyl-1H-indol-3-yl)6-nitroindolin-2-one: Light yellow solid. ; Mp: 345-347°C:^{1}H NMR (300 MHz, DMSO-d_6): δ 1.99(3H,s), 2.215(3H,s), 6.46(1H,d, J= 8.120), 6.67 (2H,t, J= 7.36), 683- 6.94(4H,m), 7.12-7.25(4H,m), 9.96(2H), 10.09(1H,s).^{13}C NMR (75 MHz, DMSO-d_6): δ 50.5; 107.2; 108.0; 108.3; 115.7; 117.3; 119.0; 123.3; 125.1; 125.3; 125.7; 129.8; 131.9; 132.8; 133.5; 138.9; 177.6. ESI-MS: m/z = 436.46$(M+H)^+$.

6e) 3,3bis(5-methoxy-1H-indol-3-yl)6-nitroindolin-2-one: Pale pink solid; Mp: >350°C:^{1}H NMR (300 MHz, DMSO-d_6): δ 3.8(6H,s) 6.93-7.00(4H,m) 7.14-7.19(2H,d, J=8.876), 7.36-7.48(4H,m) 7.67 (1H,s), 10.02(2H,s), 10.29(1H,s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.9; 55.1; 100.3; 110.8; 111.5; 111.9; 113.6; 114.0; 118.6; 123.4; 123.8; 126.5; 128.8; 127.1; 131.7; 142.4; 147.8; 153.0; 158.5. ESI-MS: m/z = 468.46$(M+H)^+$.

APPLICATION

It has many advantages like less reaction time, minimize the byproducts and better yield of the products.

CONCLUSION

In this present investigation, we report a simple and eco friendly method for the synthesis of 3,3-di indolin-2-one's and their derivatives in presence of reusable ZrO_2/ SBA-15 nano catalyst. This method has many advantages like less reaction time, minimize the byproducts and better yield of the products.

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