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Application and comparison of the catalytic activity of Fe_3O_4 MNPs, Kaolin and Montmorillonite K10 for the synthesis of indole derivatives

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Abstract

Synthesis of indole derivatives was investigated and compared to the reaction of phenylhydrazine and ketones in the presence of the heterogeneous catalysts like kaolinite, montmorillonite K10 and Fe_3O_4 MNPs in ethanol under reflux conditions. After comparing the HPLC chromatogram of products it was compared and found that kaolin and montmorillonite K10 are better and more efficient candidate than Fe_3O_4 magnetic nanoparticles for synthesis of indole derivatives. The synthesized compounds have been characterized by ^{1}H-NMR and ^{13}C-NMR. The advantages of this reaction are short reaction time, mild reaction conditions, high catalytic activity in green chemistry, increasing reaction speed without air pollution and good yields.

Keywords: Indole; phenylhydrazine; kaolinite; montmorillonite K10; Fe_3O_4 MNPs.

Introduction

Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including anticancer [1], antioxidant [2], anti-rheumatoid and anti-HIV [3,4] and also play a vital role in the immune system [5,6]. Many indole derivatives are considered as the most potent scavenger of free radicals and other biological activities [7,8]. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years [9–15]. In addition, it was reported that various 3-substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals and perfumes [16]. One of the major current challenges of chemists is to develop synthetic catalysts that are usually carried out under mild conditions with less polluting capability, being environmentally friendly and inexpensive, having high yields and selectivity, easy work-up and reusability. Heterogeneous catalysts like Fe_3O_4 MNPs [17], Kaolin [18] and Montmorillonite K10 [19] are typically more tolerant of extreme operating conditions than their homogeneous analogues. Because of these facts in this project we investigate the synthesis of indole derivatives with some heterogeneous catalysts.

Experimental

All solvents were purified and dried using established procedures. FT-IR

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measurements were recorded on a Shimadzu 8400s spectrometer with KBr plates. The HPLC chromatograms were recorded on Knauer. The NMR spectra were recorded on Bruker XL 400 (400 MHz) instruments. Besides, Melting points were determined on an Electrothermal 9100 without further corrections.

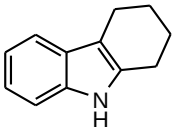
Preparation of Fe_3O_4 MNPs

Fe_3O_4 MNPs were prepared according to the previously reported procedures [20-22].

General procedure for synthesis of indole derivatives

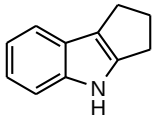
Carbonyl compound (1mmol) and phenyl hydrazine (1mmol) were mixed in ethanol (5ml), and then heterogeneous catalyst (0.07g) was added. The mixture was vigorously stirred under reflux condition for 1h. The progress of the reaction was monitored by TLC using *n*-hexane–ethyl acetate (5:1) and detected by UV lamp (254 & 366 nm). At the end of the reaction, the catalyst was recovered by filtration (Fe_3O_4 MNPs were recovered using an external magnet), washed with EtOH, dried at 60 °C for 1 h and reused four times for the same reaction. The residue of the reaction mixture was evaporated, and the crude product was purified by short column chromatography on silica gel (eluent: *n*-hexane: EtOAc / 5:1).

2,3,4,9 -Tetrahydro-1H- [23] carbazole



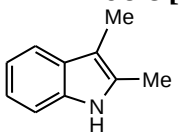
Colorless solid; Yield 97%; M.p. 118–120 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75–1.90 (m, 4H), 2.60–2.71 (m, 4H), 6.96–7.07 (m, 2H), 7.18 (dd, 1H, *3J* = 7.6, 1.6 Hz) 7.38 (d, 1H, *3J* = 7.6 Hz), 7.55 (s, 1H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 21.0, 23.3, 23.4, 110.3, 110.5, 117.8, 119.2, 121.1, 128.0, 134.2, 135.8.

1,2,3,4-Tetrahydrocyclopenta[b]indole [23]



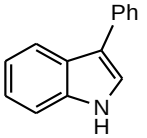
Colorless solid; Yield 92%; M.p. 101–103ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51–2.61 (m, 2H), 2.81–2.96 (m, 4H), 7.07– 7.14 (m, 2H), 7.28–7.33 (m, 1H), 7.43–7.48 (m, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 26.0, 28.8, 111.4, 118.6, 119.6, 119.9, 120.6, 124.9, 141.1, 143.8.

2, 3-Dimethyl-1H-indole [24]



Colorless solid; Yield 88%; M.p. 104–106ºC; ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.20 (s, 3H), 6.95–7.05 (m, 2H), 7.06–7.12 (m, 1H),7.33–7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.5, 11.6, 107.1, 110.2, 118.0, 119.1,121.0, 129.5, 130.8, 135.3.

3-Phenyl-1H-indole [26]

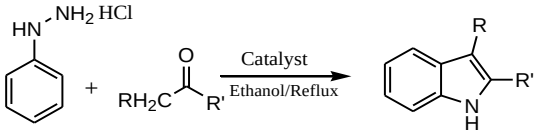


Colorless solid; Yield 87%; M.p. 85–86ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.32 (m, 3H), 7.33 (d, 1H, *3J* = 2.8 Hz), 7.39–7.51 (m, 3H), 7.65–7.75 (m, 2H), 7.95 (d, 1H, *3J* = 7.6 Hz), 8.19 (br s, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 111.5, 118.5, 119.9, 120.4, 121.9, 122.5, 125.9, 126.1, 127.6,128.9, 135.7, 136.8.

Result and discussion

In this article, it was reported that nano Fe_3O_4, kaolin and montmorillonite K10 are used for the synthesis of indole derivatives. They are highly efficient and eco-friendly catalysts for the synthesis of organic compounds. The reaction mixture of phenyl hydrazine and ketone was stirred under reflux condition in the presence of the other catalyst and monitored by TLC in *n*-hexane: ethylacetate / 5:1. The reflux continued 1 hour to complete the reaction (Scheme 1).



Scheme 1. Synthesis of indole derivatives

The product from the other catalyst was compared to HPLC chromatograms and identified by NMR spectra and physical data with those of authentic samples.

In the preliminary stage of the investigation the model reaction of phenylhydrazine and cyclopentanone was carried out using various amounts of Fe_3O_4 nanoparticles, kaolin, and montmorillonite K10 in various solvents and conditions.

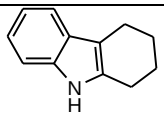
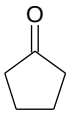
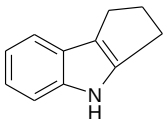
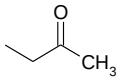
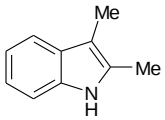
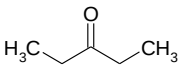
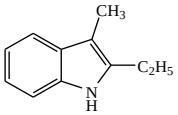
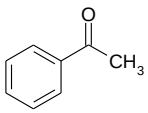
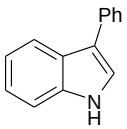
The optimum amount of nano-Fe_3O_4 was 0.07g as shown in Table1. It was found that in the absence of Fe_3O_4 magnetic nanoparticles, the only trace of the desired product was observed on TLC plate even after 4h of reaction. When the reaction was performed in the presence of kaolin and montmorillonite K10, it proceeded to give the desired product. The best results were obtained with 0.07g of kaolin and montmorillonite K10 in ethanol under reflux conditions (Table 1, Entries 23-25). Increasing the amount of catalyst does not improve the yield of the product any further, whereas decreasing the amount of catalyst leads to decrease in the product (Table 1, Entries 24 and 26). To evaluate the scope and limitations of this methodology, we extended our studies to include a variety of structurally different carbonyl compounds produced the corresponding indole derivatives. In almost all cases, the reactions proceeded smoothly within 1hour in ethanol to give indole derivatives provides the corresponding products in good isolated yields without formation of any side products. The structures of compounds were determined by NMR. They were in full agreement with the proposed structures.

Table 1. The reaction of phenyl hydrazine (1mmol) and cyclopentanone (1 mmol) under different conditions

Entry	Solvent	Catalyst	Catalyst (g)	Time (h)	Yield[a] (%)
1	THF	-	-	4	trace
2	THF	Fe_3O_4 MNPs	0.03	4	trace
3	THF	Fe_3O_4 MNPs	0.05	2	45
4	THF	Fe_3O_4 MNPs	0.07	2	48
6	THF	K10	0.07	1	83
7	THF	Kaolin	0.07	1	81
8	CH_3CN	-	-	4	42
9	CH_3CN	Fe_3O_4 MNPs	0.07	2	50
10	CH_3CN	K10	0.07	2	81
11	CH_3CN	Kaolin	0.07	2	77
12	*n*-Hexane	-	-	4	trace
13	*n*-Hexane	Fe_3O_4 MNPs	0.07	3	48
14	*n*-Hexane	K10	0.07	3	48
15	*n*-Hexane	Kaolin	0.07	3	47
16	EtOH	-	-	4	trace
17	EtOH	Fe_3O_4 MNPs	0.07	1	51
18	EtOH	Fe_3O_4 MNPs	0.06	1	50
19	EtOH	Fe_3O_4 MNPs	0.03	2	trace
23	EtOH	K10	0.07	1	92
24	EtOH	K10	0.10	1	91
25	EtOH	Kaolin	0.07	1	89
26	EtOH	Kaolin	0.10	1	90
27	%50 EtOH	Fe_3O_4 MNPs	0.07	1	48
28	%50 EtOH	K10	0.07	1	76
29	%50 EtOH	Kaolin	0.07	1	74

[a]Isolated yield

Table 2. Synthesis of indole derivatives using different catalysts

Entry	ketone	product	Yield% Fe_3O_4 MNPs	Yield% Kaolin	Yield% Montmorillonite K10
1		 [23]	64	95	97
2		 [23]	51	89	92
3		 [24]	72	83	82
4		 [25]	69	81	88
5		 [26]	72	82	82

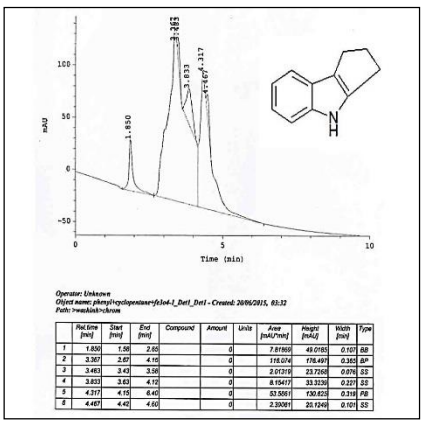


Figure 1. HPLC Chromatogram of 1,2,3,4-Tetrahydrocyclopenta[b]indole using Fe_3O_4 MNPs

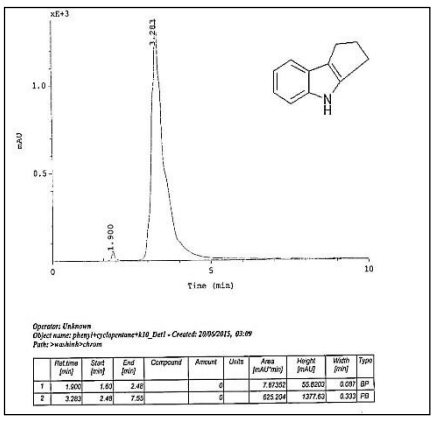


Figure 2. HPLC Chromatogram of 1,2,3,4-Tetrahydrocyclopenta[b]indole using montmorillonite K10

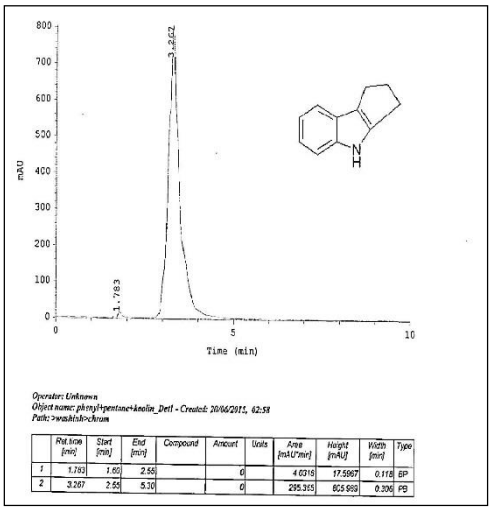


Figure 3. HPLC Chromatogram of 1,2,3,4-Tetrahydrocyclopenta[b]indole using Kaolin

Phenyhydrazine was reacted with cyclopentanone in the presence of Fe_3O_4 MNPs, kaolin and montmorillonite K10. The HPLC chromatograms of these reactions (Figure 1-3) were compared and it was found that kaolin and montmorillonite K10 are better and more efficient candidates than Fe_3O_4 magnetic nanoparticles for the synthesis of 1,2,3,4-Tetrahydrocyclopenta[b]indole.

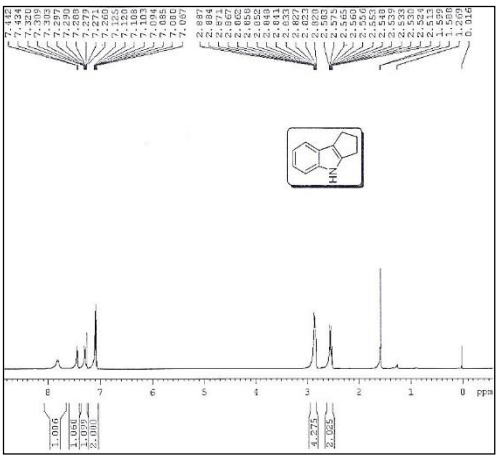


Figure 4. ^{1}H-NMR spectra of 1,2,3,4-Tetrahydrocyclopenta[b]indole

The ^{1}H-NMR spectra of 1,2,3,4-Tetrahydrocyclopenta[b]indole exhibited broad signal for NH proton at 7.44 ppm. Three CH_2 protons exhibited signals at 2.55 and 2.85 ppm. Four aromatic protons exhibited as doublet and two multiplet protons at 7.07-7.43 ppm (Figure 4).

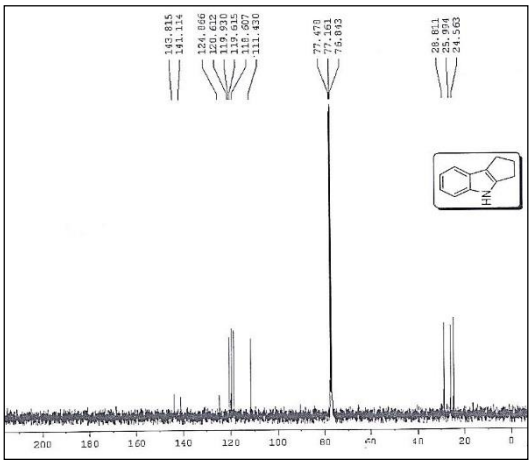
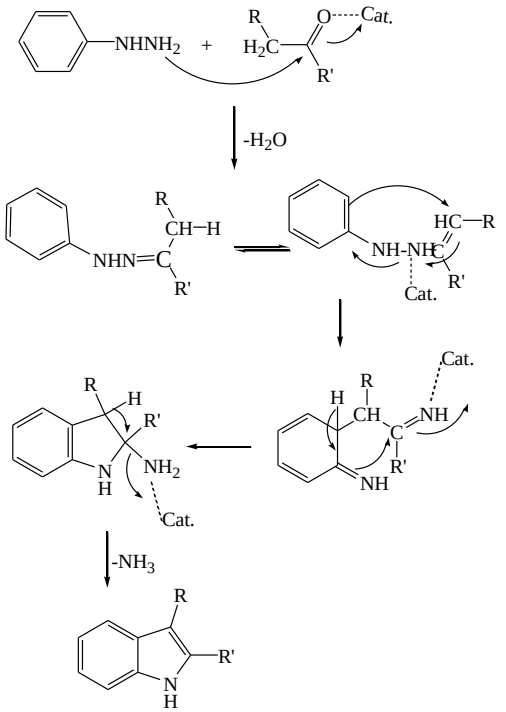


Figure 5. ^{13}C-NMR spectra of 1,2,3,4-Tetrahydrocyclopenta[b]indole

^{13}C-NMR of compound 1,2,3,4-Tetrahydrocyclopenta[b]indole indicates sharp signals for CH_2 carbons at 24.563, 25.994 and 28.811 ppm. The signal attributed to unsaturated carbons double bond (-C=C-NH) appears at 141.114 and 143.815 ppm (Figure 5).

A plausible mechanism for the reaction is envisaged in scheme 2. Carbonyl group is first activated by catalysts then the nitrogem of phenyl hydrazine attacks the positive center to afford phenylhydrazone intermediate. Imine bond in hydrazone is activated by catalysts to provide more positive center for intermolecular cyclization and production of indole.



Scheme 2. The probable mechanism for synthesis of indole derivatives

Table 3. Recycling of the catalysts for synthesis of 1,2,3,4-Tetrahydrocyclopenta[b]indole

Number of cycle	Fe_3O_4 MNPs Yield[a] (%)	Kaolin Yield[a] (%)	K10 Yield[a] (%)
1	51	89	92
2	50	89	90
3	48	83	88
4	44	80	85

The catalyst was simply recovered by filtration– or using an external magnetic field for Fe_3O_4 MNPs– washed with ethanol, and dried. The recovered catalyst was then added to a fresh reaction mixture under the same conditions and reused 4 times without significant loss of activity (Table 3). Further recycling of the catalyst led to gradual loss of the catalyst during the recovering and washing stages.

Conclusion

In summary, an efficient and environmentally friendly method for synthesis of indole derivatives was described. The reactions were performed under reflux condition and the corresponding products were afforded in good to excellent yields. Also, Kaolin and montmorillonite K10 are found to be more efficient for synthesis of indole derivatives. The advantages of this method are short reaction time, simple work-up procedure, ease of separation, high conversion, easier and less expensive than the other methods.

Acknowledgments

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