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RESEARCH ARTICLE

A SIMPLE AND EXPEDITIOUS NICKEL (II) FERRITE CATALYZED GREEN SYNTHESIS OF ALKYL AND ARYL BIS (INDOLYL) METHANE UNDER SOLVENT FREE MICROWAVE CONDITION

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ABSTRACT

NiFe₂O₄ as an efficient, recyclable and eco-benign heterogeneous catalyst has been investigated for green and expeditious synthesis of alkyl and aryl bis(indolyl)methane under solvent free microwave condition in good to excellent yields. Magnetic NiFe₂O₄ nano particles can be recovered by external magnet and reused for five times without appreciable change in catalytic activity. Advantages of present protocol includes shorter reaction time, no use of hazardous solvent, cleaner work up, high yields and reusability of catalyst thus making this approach environmentally more acceptable and applicable in the field of green synthesis.

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INTRODUCTION

Synthesis of bis (indolyl) alkane has attracted a large number of researches because of their wide occurrence in various nature products (Potter *et al.* 1977, Osawa *et al.* 1998, Fahy *et al.* 1991, Bell *et al.* 1994, Garbe *et al.* 2000, Morris *et al.*, Bifulco *et al.* 1995) possessing biological and pharmaceutical activity (Zeligs *et al.* 1998, Michnovics *et al.* 1993, Bell *et al.* 2000). Bis (indole) methanes (BIM) are the highly active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in cancer cells of men and women (Yanni *et al.* 1996, Bandgar *et al.* 2004). Moreover BIM may show decreased abnormal cell growth associated with cervical dysplasia (Michnovics *et al.* 1993, Bell *et al.* 2000). Thus the development of high thought full methods for synthesis of BIM have received increasing attention in view of their versatile biological pharmacological activities (Abdelbaqi *et al.* 2011, Andey *et al.* 2014, Li *et al.* 2012, Rogan 2006, Kobayashi *et al.* 1994, Sivaprasad *et al.* 2006, Sujata *et al.* 2009). Consequently a large number of methods have been developed for the synthesis of bis(indolyl)methanes, among them acid catalyzed electrophilic substituted reaction of indoles with aldehydes is one of the most straight forward approaches. Recently various reagents and catalyst have been employed to achieve the desired transformations include.

CuBr₂ (Mo *et al.* 2005), CAN (Zeng *et al.* 2005), NBS (Koshima *et al.* 2002), BF₃.Et₂O (Chatterjee *et al.* 1980), ZrCl₃ (Nagrajan *et al.* 2002), Dy(OTf)₃ (Mi *et al.* 2004), surfactant (Zolfigol *et al.* 2007, Deb *et al.* 2006), HY-Zeolite (Reddy *et al.* 2003), silica sulphuric acid (Pore, *et al.* 2006), Zeokarb 225 (Magesh *et al.* 2004), P₂O₅/SiO₂ (Hasaninejad *et al.* 2007), LiClO₄ (Yadav *et al.* 2001). However few reports are available under green methodologies involving the use of ion-exchange resin (Feng *et al.* 2004), ionic liquids (Ji *et al.* 2003; Ji S., and Gu *et al.* 2004) in conjugation with In(OTf)₃ (Nagarajan *et al.* 2002), Zirconia (Silveira *et al.* 2009), additional use of microwave (Xia *et al.* 2004) and ultrasonic irradiation in glycerol (Mendes *et al.* 2015). Few drawbacks of the reported strategies involve the use volatile toxic organic solvents and reagents, elevated temperature, tedious work up, less yields, prolonged reaction time and moisture sensitive expensive catalysts. Keeping the above facts in mind and our keen interest in the development of green approach towards applications of environment benign catalyst in organic synthesis (Bansal *et al.* 2017, Pippal *et al.* 2017, Sharma *et al.* 2011). We herein report the simple, expeditious, solvent free, atom economic green synthesis of alkyl and aryl BIM by using environment benign magnetically separable reusable catalyst in microwave conditions.

MATERIALS AND METHODS

All the solvents and reagents were used as such as supplied from Merck (Darmstadt, Germany) and S.D. Fine-chem

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(Mumbai, India). FTIR spectra were recorded in KBr on a Shimadzu FTIR 8401 spectrometer. ^1H and ^{13}C spectra were recorded on a Bruker DRX 300 spectrometer operating at 300MHz for ^1H NMR and 75MHz for ^{13}C NMR solutions in CDCl_3 and $\text{DMSO-}d_6$. The ESI mass spectra were measured on waters UPLC-TDQ spectrometer. TLC was performed on silica coated glass plates; spots were developed in I_2 Chamber or visualized in UV chamber. The morphology of the catalyst was studied by high resolution electron microscopy HRTEM-300 KV Technai G2 30 S TWIN with gold coating equipped with energy dispersive X-ray spectroscopy. Melting points were recorded on digital Scientech instrument using capillary method and are uncorrected. A CEM Discover microwave was used for irradiation purpose.

Typical procedure for the synthesis of NiFe_2O_4 magnetic nanoparticle

Synthesis of NiFe_2O_4 magnetic nanoparticles the mixture of nickel nitrate (1 equiv), sugar (17 equiv), $\text{Fe}_2(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (equiv), monoethanolamine (25 equiv), HNO_3 (44 equiv), and double distilled water (300mL) in a beaker was heated in a hot plate up to the dryness.

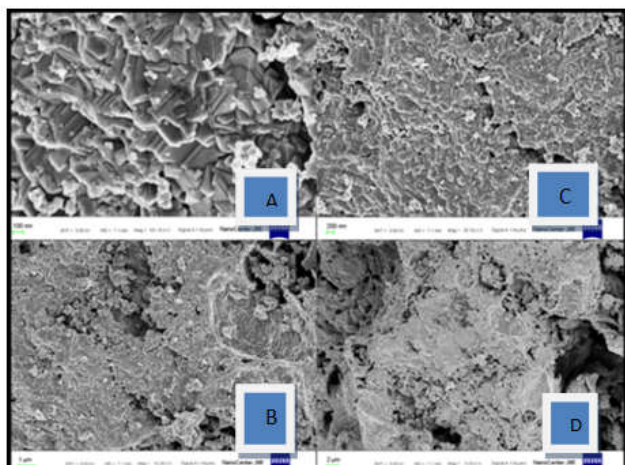


Figure 1. HRTEM image of NiFe_2O_4 MNP's

The black residue obtained was kept in preheated muffle furnace at 800°C for 6-7hrs. The resulting brown colored powder was further characterized by XRD, SEM with EDX Data and FTIR. The high resolution electron microscopy (HRTEM) of NiFe_2O_4 MNP'S is shown in Figure 1. The particle size of the nickel ferrite NP's sample is typically in the range of 100-200nm. The small crystallize are irregular in shape and are attached to each other along the grain boundaries. The material was verified by XRD data which matched very well with standard data. Size of crystallite was found by 100nm from analysis of XRD profile by Debye Sheerer equation surface area was found to be $14\text{m}^2/\text{gm}$ Figure 2.

General procedure for the synthesis of bis(indolyl)methane

A mixture of aldehyde (1.0 equiv.), indole (2.0 equiv.) and NiFe_2O_4 (10 mol%) were mixed thoroughly at room temperature and afterwards the mix was intermittently irradiated in a microwave for the appropriate time period. The reaction was monitor by TLC.

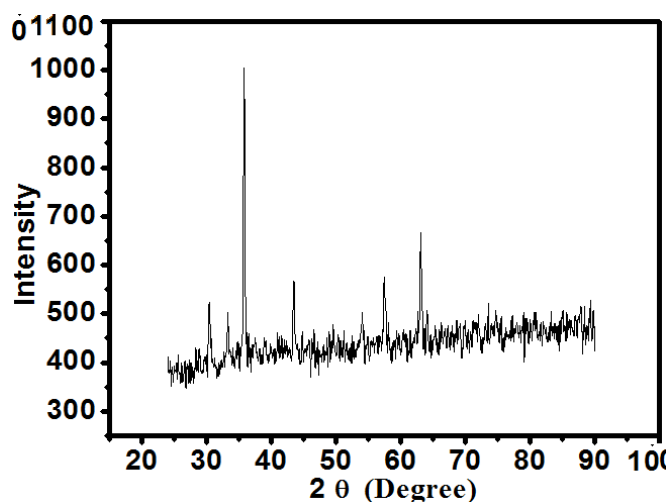
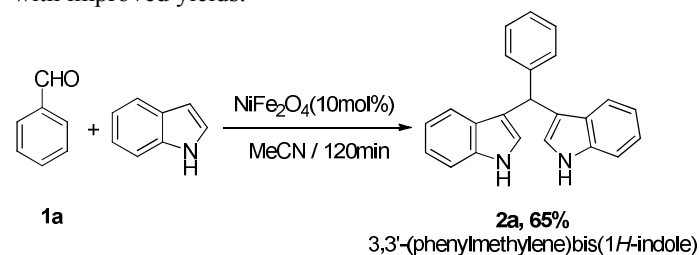


Figure 2. XRD image of NiFe_2O_4 MNP's

On completion of reaction, the mixture was diluted with EtOAc, catalyst was removed by external magnet. The residue left was concentrated over rotatory evaporator and crude product was purified by column chromatography to afford the pure bis (indolyl)methane products. All the synthesized compounds were fully characterized by FTIR, NMR (^1H and ^{13}C) and mass spectrometer.

RESULTS AND DISCUSSION

In our initial, efforts, benzaldehyde 1a was taken as a model for reaction with indole (Scheme 1). Benzaldehyde (1.0 equiv.), indole (2.0 equiv.) and NiFe_2O_4 catalyst (10 mol%) was refluxed in CH_3CN for 120 min. On completion of reaction the desired product 3,3'-(phenylmethylene)bis(1H-indole) 2a was isolated in 65% of yields exhibiting the catalytic property of catalyst (scheme 1, Table 1 and entry 1). Encouraged by the above result, we then aimed to reduce the reaction time, eliminate the use of toxic solvent and product with improved yields.



Scheme 1. Synthesis of 2a using NiFe_2O_4 catalyst

In this aspect the model reaction was irradiated under microwave at 600W in solvent free condition. To our delight the reaction was completed in just 90 seconds giving the product 2a with improved yield of 87% (Table 1, entry 3). In order to optimize the finest reaction condition, same model reaction was performed at various wattage of microwave, with different amount of catalyst loading. When the model reaction was performed in absence of catalyst at 600W the product was isolated in very poor yields (Table 1, entry 4). Fixing the wattage at 300W and on subsequent increase in catalyst loading improved the yield to some extent and reaction time also (Table 1, entries 5-8). Further increase of wattage and catalyst loading yielded the products into appreciable good amount (table1, entries 9-11). Reaction at 900W and 20mol% of catalyst loading could not improve the yield further (Table

1, entry 11) substantially. The product obtained at our optimized reaction condition (Table 1, entry 3) gave the best yield.

Table 1. Optimization of finest reaction condition for the synthesis of BIM

Entry	NiFe ₂ O ₄ (mol%)	Power (W)	Time (Sec)	Yield (%) ^a
1	10 ^b	-	2hr	65
2	No Catalyst ^c	-	2hr	10
3	10	600	90	87
4	No catalyst	600	120	27
5	2	300	300	43
6	5	300	300	52
7	10	300	240	65
8	20	300	240	67
9	5	600	300	51
10	20	600	90	86
11	20	900	86	86

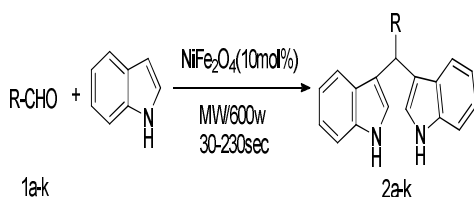
^aisolated yield

^bbenzaldehyde (1.0 mol), indole (2.0 mol) refluxed in MeCN for 2.0 hrs in taking 10 mol% of NiFe₂O₄ catalyst

^cbenzaldehyde (1.0 mol), indole (2.0 mol), refluxed in CH₃CN for 2.0 hrs in absence of catalyst.

To establish the generality and applicability of this method, indole was condensed with structurally diverse aldehydes to furnish substituted BIM in high to excellent yield in short reaction time. The results obtained are summarized in Table 2.

Table 2. NiFe₂O₄ catalysed synthesis of BIM's derivatives



Entry	R	Time(sec)	Product	Yield(%) ^a	Melting point (°C)	
					our	Lit.
1	C ₆ H ₅	90	2a	87	124-25	126-27 (Li, S and Wang et al. 2004)
2	4-MeC ₆ H ₄	130	2b	85	92-93	89-91 (Shirri et al. 2013)
3	4-OHC ₆ H ₄	150	2c	88	122-24	124-26 (Mishra et al. 2011) ⁴⁶
4	4-OMeC ₆ H ₄	180	2d	88	190-92	187-89 (Li S and Zhou et al. 2004) ⁴⁷
5	3,4-OMeC ₆ H ₃	200	2e	82	196-98	198-99 (Yadav J.S. and Reddy et al. 2001) ⁴⁸
6	4-NO ₂ C ₆ H ₄	30	2f	92	122-24	127-28 (Feng X. L. and Quan et al. 2004) ⁴⁹
7	4-ClC ₆ H ₄	38	2g	91	80-81	78-80 (Reddy et al. 2003) ⁵⁰
8	3-ClC ₆ H ₄	38	2h	91	83-85	81-83 (Li Ji-Tai et al. 2010) ⁵¹
9	4-BrC ₆ H ₄	55	2i	89	119-20	116-17 (Olyaei et al. 2013) ⁵²
10	C ₅ H ₁₁	230	2j	85	63-64	65-66 (Hojati et al. 2013) ⁵³
11	C ₇ H ₁₅	230	2k	86	-	-

^aisolated yields

Aldehydes bearing electron withdrawing substituent on the aromatic ring took less time for completion of reaction and

yielded the bis-indolyl products in very good yields (Table 2, entries 6-9). Whereas aldehydes with electron donating groups took comparatively little more reaction time for the completion without affecting yielding the products in good yields. (Table 2, entries 1-5). However aliphatic aldehydes needed longer reaction time and afforded the products in appreciable yields (Table 2, entries 10-11). This may be attributed to the lower boiling points of aliphatic aldehydes.

Recovery and reusability of catalyst

To augment our investigation, we checked the recyclability of NiFe₂O₄ catalyst by reusing the magnetically separated catalyst from the reaction mixture. The catalyst was reused for five times (Fig. 3) and no appreciable change in catalytic activity was noticed.

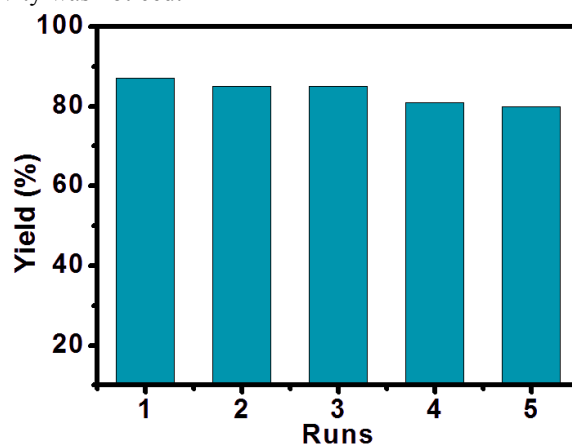


Fig. 3. Reusability of catalyst

Conclusions

Magnetic nano particles of NiFe₂O₄ may be used as heterogeneous, cheaper and efficient catalyst for the synthesis of BIM under solvent free microwave condition. The milder reaction condition, shorter reaction time, higher yields, easy work up and reusability of catalyst are the main advantages of the green protocol developed.

2a) 3,3'-(phenylmethylene)bis(1H-indole) pink solid; ¹H NMR (500 MHz, CDCl₃) δ 7.91 (br s, 2H, NH), 7.39 (d, 2H, J = 8.0, Ph-H), 7.36 (d, 2H, J = 8.0, Ph-H), 7.35 (d, 2H, J = 7.0, Ph-H), 7.28 (t, 2H, J = 7.0, Ph-H), 7.22-7.19 (m, 1H, Ph-H), 7.17 (t, 2H, J = 7.0, Ph-H), 7.00 (t, 2H, J = 7.5, Ph-H), 6.66 (d, 2H, J = 1.5, Py-H), 5.89 (s, 1H, CH); ¹³C NMR (125 MHz, CDCl₃) δ 144.2, 136.9, 128.9, 128.4, 127.2, 126.3, 123.8, 122.1, 120.1, 119.9, 119.4, 111.2, 40.4; MS, m/z (%): 322 (5%, M⁺), 320 (90, [M-2H]⁺), 243 (90), 77 (90), 29 (90).

2b) 3,3'-(p-tolylmethylene)bis(1H-indole) red solid; ¹H NMR (500 MHz, CDCl₃) δ 7.70 (br s, 2H, NH); 7.37 (d, 2H, J = 8.0, Ph-H), 7.27 (d, 2H, J 8.5, Ph-H), 7.20 (d, 2H, J = 8.0, Ph-H), 7.14 (t, 2H, J 7.5, Ph-H), 7.06 (d, 2H, J = 8.0, Ph-H), 6.98 (t, 2H, J 7.5, Ph-H), 6.55 (d, 2H, J = 2.0, Ph), 5.82 (s, 1H, CH), 2.30 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 141.1, 136.8, 135.7, 129.1, 128.7, 127.2, 123.7, 122.0, 120.1, 120.0, 119.3, 111.2, 39.9, 21.2; MS, m/z (%): 336 (5%, M⁺), 334 (87, [M-2H]⁺), 243 (83), 143 (76), 29 (77).

2c) 4-(di(1H-indol-3-yl)methyl)phenol. pink solid; ¹H NMR (500 MHz, DMSO-d₆) δ 10.76 (d, 2H, J 1.5, NH), 9.15 (s, 1H, OH), 7.33 (d, 2H, J 8.0, Ph-H), 7.25 (d, 2H, J 8.0, Ph-H), 7.13 (d, 2H, J 8.5, Ph-H), 7.02 (t, 2H, J 7.5, Ph-H), 6.84 (t, 2H, J

7.5, Ph-H), 6.77 (d, 2H, J 2.0, Ph-H), 6.65 (d, 2H, J 8.5, Ph-H), 5.70 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO- d_6) δ 155.3, 136.6, 135.2, 129.1, 126.7, 123.4, 120.8, 119.2, 118.7, 118.1, 114.8, 111.4; MS, m/z (%): 338 (36%, M^+), 336 (99, $[\text{M}-2\text{H}]^+$), 242 (100), 117 (37), 65 (10).

2d) 3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) red solid; IR (KBr) ν/cm^{-1} 3395, 2924, 1509, 1454, 1245, 741; ^1H NMR (300 MHz, CDCl_3) δ 7.86 (br s, 2H, NH), 7.43 (d, 2H, J = 7.8, Ph-H), 7.37 (d, 2H, J = 7.8, Ph-H), 7.27-7.30 (m, 2H, Ph-H), 7.21 (t, 2H, J = 7.2, Ph-H), 7.05 (t, 2H, J = 7.2, Ph-H), 6.86 (d, 2H, J = 8.4, Ph-H), 6.64 (s, 2H, Py-H), 5.88 (s, 1H, CH), 3.82 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 157.92, 136.72, 136.26, 129.64, 127.09, 123.56, 121.91, 120.05, 120.01, 119.21, 113.60, 111.006, 55.24, 39.36; MS, m/z (%): 352 (11%, M^+), 350 (98, $[\text{M}-2\text{H}]^+$), 243 (93), 117 (34), 77 (18), 29 (62).

2f) 3,3'-((4-nitrophenyl)methylene)bis(1H-indole) yellow solid; ^1H NMR (500 MHz, DMSO- d_6) δ 10.95 (br s, 2H, NH), 8.15 (d, 2H, J = 8.0, Ph-H), 7.61 (d, 2H, J = 8.0, Ph-H), 7.37 (d, 2H, J = 7.5, Ph-H), 7.29 (d, 2H, J = 7.5, Ph-H), 7.06 (t, 2H, J = 7.0, Ph-H), 6.90 (s, 2H, Ph-H), 6.89 (t, 2H, J = 7.0, Ph-H), 6.03 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO- d_6) δ 153.1, 145.7, 136.6, 129.4, 126.3, 123.9, 123.4, 121.1, 118.9, 118.4, 116.7, 111.6; MS, m/z (%): 367 (52%, M^+), 365 (100, $[\text{M}-2\text{H}]^+$), 317 (48), 121 (20), 117 (44).

2g) 3,3'-((4-chlorophenyl)methylene)bis(1H-indole) reddish brown solid; IR (KBr) ν/cm^{-1} 3408, 2922, 1455, 1089, 742; ^1H NMR (500 MHz, CDCl_3) δ 7.79 (br s, 2H, NH), 7.34 (d, 2H, J = 7.5, Ph-H), 7.30 (d, 2H, J = 7.5, Ph-H), 7.24-7.20 (m, 4H, Ph-H), 7.16 (t, 2H, J = 7.5, Ph-H), 7.00 (t, 2H, J = 7.5, Ph-H), 6.55 (d, 2H, J = 2.0, Ph-H), 5.83 (s, 1H, CH); ^{13}C NMR (125 MHz, CDCl_3) δ 142.7, 136.8, 131.9, 130.2, 128.5, 127.0, 123.8, 122.2, 120.0, 119.5, 119.3, 111.3, 39.8; MS, m/z (%): 357 (50%, M^+), 355 (76, $[\text{M}-2\text{H}]^+$), 291 (6), 244 (76), 117 (74), 71 (75).

2h) 3,3'-((3-chlorophenyl)methylene)bis(1H-indole) reddish brown solid, IR= (KBr, cm^{-1}): 3412, 3300, 2978, 2673, 2499, 1911, 1618, 1591, 1487, 1375, 1267, 1085, 860; ^1H NMR (300 MHz, CDCl_3): 5.85(s, 1H); 6.83-6.89(m, 4H); 7.01-7.07(m, 1H); 7.26-7.37(m, 4H); ^{13}C NMR (75MHz, CDCl_3): 170.51, 144.07, 136.70, 130.39, 130.19, 128.08, 126.57, 123.69, 121.08, 119.10, 118.38, 117.68, 111.60, 59.88, 14.15.; (ES/MS): (M^+ -116) -240(100%).

2i) 3,3'-((4-bromophenyl)methylene)bis(1H-indole) yellow solid; MS, m/z (%): 401 (27%, M^+), 399 (27, $[\text{M}-2\text{H}]^+$), 243 (16), 116 (100), 28 (58). Anal. Calc. for $\text{C}_{23}\text{H}_{17}\text{BrN}_2$: C 68.84, H 4.27, N 6.98. Found: C 68.55, H 4.62, N 6.80%.

2j) 3,3'-((hexane-1,1-diyl)bis(1H-indole))colorless solid; MS, m/z (%): 316 (13%, M^+), 314 (12, $[\text{M}-2\text{H}]^+$), 243 (90), 214 (22), 116 (100), 43 (90), 29 (90).

2k) 3,3'-((octane-1,1-diyl)bis(1H-indole)) Thick liquid; MS, m/z (%): 344 (3%, M^+), 342 (70, $[\text{M}-2\text{H}]^+$), 243 (100), 129 (68), 57 (68), 29 (68).

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