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Magnetically separable sulfonic acid catalysed one-pot synthesis of diverse indole derivatives

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ARTICLE INFO ABSTRACT Article history: Fe₃O₄-OSO₃H was identified as efficient reusable catalyst for the facile synthesis of Received diarylmethyl indole derivatives under neat condition by C-C bond forming reaction. Fe₃O₄-Received in revised form OSO3H catalysis was further extended to C-N bond forming reactions and for the synthesis of Accepted spermicidal 3,3'-di(indolyl)oxindole derivative. All the products were obtained in good to Available online excellent yield. 2009 Elsevier Ltd. All rights reserved. Keywords: Diarylmethyl indole Bioactive molecule Iron oxide Aminoalkylated indole di(indolyl)oxindole

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1. Introduction

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Multicomponent reactions circumvent step-wise iterative synthesis to access densely functionalized bioactive skeletons by forming multiple bonds in a single step.¹ Solvent-free multicomponent reactions gained significant attention in green organic synthesis and Sheldon acclaimed solvent-free reactions as "The best solvent is no solvent".² Use of magnetically separable and reusable catalyst in a solvent-free multicomponent reaction fulfils multiple green synthesis requirements such as use of recyclable catalyst, employing less hazardous solvent, achieving high atom economy, reducing the number of reaction steps etc.





Use of aforementioned conditions in substituted indole synthesis is desirable since indole derivatives possess antiviral,³ anti-HIV,⁴ anti-cancer,⁵ antiproliferative,⁶ antibacterial,⁷ cytotoxic,⁸ antitubercular⁹ and antiinflammatory activities (Fig. 1).¹⁰

Iron oxides as well as functionalized iron oxides have been widely used in reactions such as Hantzsch,¹¹ Mannich,¹² Sonogashira–Hagihara,¹³ Biginelli,¹⁴ Suzuki,¹⁵ Ugi¹⁶ and for the synthesis of chromenes, pyrimidines and epoxide derivatives.¹⁷⁻¹⁹ Recently, Firouzabadi and co-workers reported functionalized Fe₃O₄ catalysed bis(indolyl)methane synthesis (Scheme 1).²⁰



Scheme 1. Fe_3O_4 catalysed bis(indolyl)methane synthesis.

However, reaction of two different nucleophiles such as indole and *N*,*N*-dimethylaniline with benzaldehyde may result in the formation of mixture of homocoupled by-products along with diarylmethyl indole derivative (Scheme 2). Previously reported diarylmethyl indoles synthesis required the use of stoichiometric quantities of either $ZnCl_2^{21}$ or $CuCl_2^{22}$ reagents. Both bis(ethylcyclopentadienyl)zirconium perfluorooctanesulfonate²³ and FeCl₃²⁴ were reasonably successful to carry out diarylmethyl indoles synthesis in catalytic quantities. However, the scope of these catalysts are marred by the use of carcinogenic 1,2-dichloroethane as solvent and prolonged reaction time for completion. Hence it is envisaged that Fe₃O₄ catalysed diarylmethyl indole synthesis in an environmentally benign medium is worth investigating.



Scheme 2. Fe₃O₄ catalysed diarylmethyl indole synthesis.

2. Results and discussion

Magnetic Fe_3O_4 nanoparticles were prepared through aqueous co-precipitation method²⁵ and are characterized by powder XRD technique (see electronic supporting information). Fe_3O_4 (10 mol%) catalyzed synthesis of diarylmethyl indole under neat condition at 100 °C gave the product **3a** in 34% yield along with the corresponding bis(indolyl)methane by-product (Scheme 3). Attempts to improve the reaction yield by varying the reaction temperature, modifying substrate to catalyst mole ratio didn't improved the reaction outcome. The poor product yield could be attributed to the mild acidic nature of Fe_3O_4 nanoparticles.



Scheme 3. Fe₃O₄ and sulfonic acid catalysed diarylmethyl indole synthesis.

It was previously reported in the literature that sulfonic acid derivatives are good catalyst for the substituted indole derivatives synthesis.²⁶ Replacement of Fe₃O₄ catalyst with *p*-toluenesulfonic acid gave **3a** in 37% yield along with 31% of bis(indolyl)methane. Use of chlorosulfonic acid improved the product **3a** yield to 48% along with the formation of 28% of bis(indolyl)methane by-product (Scheme 3). Though the later result is encouraging, chlorosulfonic acid is corrosive, hygroscopic and lachrymatory in nature. Moreover, it reacts violently with water to form HCl and H₂SO₄. Hence, we have decided to synthesize and investigate catalytic potential of sulfonic acid anchored Fe₃O₄ nanoparticles (Fe₃O₄-OSO₃H). Fe₃O₄-OSO₃H was synthesized by closely following a literature procedure and the product was obtained as fine brown powder (Scheme 4).²⁷



Scheme 4. Synthesis of sulfonic acid functionalized Fe₃O₄

The formation of sulfonic acid embedded Fe_3O_4 was confirmed by comparing IR spectrum of Fe_3O_4 before and after functionalization (Figure 2A-B). The presence of characteristic peaks at 3341, 1623 and 1208 cm⁻¹ confirms the presence of sulfonic acid moiety on the surface of Fe_3O_4 (Figure 2B). SEM analysis of the Fe_3O_4 -OSO₃H showed the materials are of ~ 23 nm dimension (Figure 2C-D). The clustering nature of Fe_3O_4 -OSO₃H in SEM analysis could be due to the hydrogen bonding interaction between the sulfonic acid functional groups.²⁷ The sulfonic acid loading on Fe_3O_4 was found to be 0.70 mmol g⁻¹ by carrying out the following experiment.²⁸ To an aqueous solution of 25 mL of 1M NaCl (pH 6.32), 100 mg of Fe_3O_4 -OSO₃H was added and stirred for 2 hours. The pH of the solution was decreased into pH 2.60. To this solution, known excess of NaOH

was added and the solution was titrated against addition of standard 0.1 M of HCl solution. From the equivalent point (9.3 mL), the loading of catalyst was found to be 0.70 mmol g^{-1} .



Figure 2. IR spectrum of (A) Fe_3O_4 (B) Fe_3O_4 -OSO₃H. SEM images of Fe_3O_4 -OSO₃H (C) at 1 μ m expansion (D) at 100 nm expansion.

	CI	Catalyst recyclability	
$\begin{array}{c} \\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \\ 1 \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c}\\ H \\ 2 \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c} H \\ 2 \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c}\\ H \end{array} \begin{array}{c} H \\ \end{array} \begin{array}{c} H \end{array} \begin{array}{c} H \end{array} \begin{array}{c} H \end{array} \begin{array}{c} H \end{array} \begin{array}{c}$	<u>100 °C, 1h</u> N H 88 %	Cycle 1 2 3 4 5	Yield(%) 88 86 86 82 77

Scheme 5. Fe₃O₄-OSO₃H catalysed 3a synthesis and catalyst recyclability studies

Table 1.	Reaction	condition	screening	for 3	3a sv	nthes
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Entry	Catalyst	Solvent	Time (h)	Yield (%) ^b
1	Fe ₃ O ₄	-	1	34
2	Fe ₃ O ₄ -OSO ₃ H	Toluene	2	8
3	Fe ₃ O ₄ -OSO ₃ H	CH₃CN	2	Traces
4	Fe ₃ O ₄ -OSO ₃ H	H₂O	2	<5
5	Fe ₃ O ₄ -OSO ₃ H	THF	2	NR ^c
6 ^d	Fe ₃ O ₄ -OSO ₃ H	-	1	88
7	Fe ₃ O ₄ -PEI ^e	-	1	NR
8	SiO₂-OSO₃H	-	3	67
9	CI-SO₃H ^f	-	1	48
10	PTSA ^g	-	1	37 ^h

^aAll the reactions were carried out with indole (1mmol), 4chlorobenzaldehyde (1 mmol), *N*,*N* dimethylaniline (1mmol) and 10 mol% of catalyst at 100 ° C. ^bYields are for the isolated products. ^cNo reaction. ^dReducing the reaction temperature to 50 °C, resulted in the formation of more amounts of bis(indolyl)methane product. ^ePolyethylenimine coated. [†]Along with product, 28% bis(indolyl)methane formed. ^g*p*-Toluenesulfonic acid. ^hReaction performed with mixture of PTSA and Fe₃O₄ gave the product in 16% yield.

 Fe_3O_4 -OSO₃H catalysed synthesis of **3a** in non-polar (toluene), polar aprotic (CH₃CN) and polar protic (H₂O) solvents gave the product in <10 % yield (Table 1, entry 2-4). The poor catalytic performance could be attributed to the sparingly soluble nature of catalyst in the aforementioned solvents. The poor catalyst solubility substantially reduces its interaction with the

substrates. Under neat condition at 100 °C, Fe_3O_4 -OSO₃H (23 mg) efficiently catalyzed one-pot synthesis of diarylmethyl indole **3a** in 88% yield (Scheme 5, Table 1, entry 6). Recyclability of the Fe_3O_4 -OSO₃H catalyst was checked for **3a** synthesis. The catalyst can be reusable up to 5 times without significant loss in catalytic activity (Scheme 5). Atomic absorption spectroscopic (AAS) studies carried out to identify the possible leaching of the iron catalyst into the reaction medium after first recycle showed only minimal leaching of iron catalyst (0.217 ppm). Elemental analysis of the spent catalyst showed a decrease in sulfur content after third cycle. This could be one of the reasons for the marginal decrease in the product yield from fourth cycle onwards.

Lewis acidic nature of the Fe₃O₄ is previously reported in the literature.^{29a-b} Synthesis of **3a** carried out with Lewis acidic Fe₃O₄ gave the product in 34% yield (Table 1, entry 1) and the Bronsted acidic chlorosulfonic acid gave 48% yield (Table 1, entry 9). Interestingly, under similar reaction conditions, Fe₃O₄-OSO₃H yielded 88% of product 3a (Table 1, entry 6). We presume, the high catalytic efficiency of Fe₃O₄-OSO₃H could be due to the combined Lewis and Brønsted acidic nature of the catalyst. Replacement of either Fe₃O₄ with SiO₂ or chlorosulfonic acid with *p*-toluenesulfonic acid substantially decrease the product yield (Table 1, entry 8,10). These results justify the synergetic effect of Fe₃O₄-OSO₃H in diarylmethyl indole synthesis. To further emphasize the significance of acidic sulphonic acid functionality on Fe_3O_4 in **3a** synthesis, basic polyethylenimine (PEI) coated Fe₃O₄ was synthesized and subjected to reaction condition (Table 1, entry 7). Fe₃O₄-PEI was found to be ineffective in 3a synthesis (Table 1, entry 7).

Fe₃O₄-OSO₃H catalysed **3a** synthesis carried out at 80 °C and 50 °C instead of 100 °C decreased the product yield (52% and 34%) and enhanced the bis(indolyl)methane by-product yield (23% and 31%). These observations are in line with the literature reports that lowering the reaction temperature favoured kinetically stable bis(indolyl)methane by-product and higher temperature resulted in the formation reaction of thermodynamically stable diarylmethyl indole product.21,22 However, unlike ZnCl₂ and CuCl₂, Fe₃O₄-OSO₃H catalysed transformation of bis(indolyl)methane to diarylmethyl indole was not observed. Increasing the catalyst loading from 23 mg to 46 mg or 69 mg didn't alter the product yield. After optimizing the reaction condition, diarylmethyl indole synthesis was screened for various substituted aldehydes (Scheme 6 and Figure 3). The reaction was found to be general for aldehydes with electron donating and electron withdrawing substituents and the products 3a-3g were obtained in appreciable yields. Aliphatic aldehyde also gave the product 3d within 30 minutes in good yield. This could be attributed to the high reactivity of formaldehyde (Scheme 6).



Scheme 6. Fe₃O₄-OSO₃H catalysed C-C bond forming reaction

After successfully finished C-C bond forming reactions, we were interested to extend this methodology to C-N bond forming reactions. Fe₃O₄-OSO₃H catalysed reaction of Indole (1mmol), 4-chlorobenzaldehyde (1mmol) and *N*-methylaniline (1mmol) under solvent-free condition gave the product within 3 h at room

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temperature itself (Scheme 7). Fe₃O₄-OSO₃H catalysed C-N bond forming reaction was found to be general for aldehydes with electron donating and electron withdrawing substituents (Figure 3). To further improve the application of this heterogeneous catalyst system, we have performed gram scale synthesis of representative **3a** and **5a** with 10 mmol of substrates and the corresponding products were obtained in 84% and 85% yields respectively.



Scheme 7. Fe₃O₄-OSO₃H catalysed C-N bond forming reaction



Figure 3. Synthesized diarylmethyl indole and aminoalkylated indole

The Fe_3O_4 -OSO₃H catalysed formation of diarylmethyl indole and aminoalkylated indole can be rationalized by the considering the following mechanism (Scheme 8).



Scheme 8. Mechanism of formation of diarylmethyl indoles and aminoalkylated indoles

Addition of *N*,*N*-dimethylaniline or *N*-methylaniline and aldehyde may result in the formation of iminium intermediate.³⁰ Nucleophilic addition of indole to the iminium intermediate could result in the formation of diarylmethyl indole and aminoalkylated indole products.

It is of interest to further extend the application of Fe_3O_4 -OSO₃H catalysis to potential bioactive skeleton synthesis. Oxindole skeletons are widely distributed in several natural products and bioactive molecules.³¹ Mondal and co-workers reported that 3,3'-di(indolyl)oxindole skeleton has good spermicidal activity.³² Fe₃O₄-OSO₃H catalysed 3,3'-di(indolyl)oxindole synthesis was not successful under neat condition. In ethanol, 3,3'-di(indolyl)oxindole was obtained in 92% yield (Scheme 9).



Scheme 9. Synthesis of 3,3'-di(indolyl)oxindole derivatives

In conclusion, we have developed an efficient and convenient method for the synthesis of diversely functionalized indole derivatives. All the products were obtained in good to excellent yield and the catalyst was reusable up to five times without much loss in catalytic activity.

Acknowledgements

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General procedure for synthesis of diarylmethylindoles:

To a stirred mixture of indole (117.5 mg, 1.0 mmol), N, N-dialkylaniline (1.0 mmol) and aldehyde (1.0 mmol), Fe₃O₄-OSO₃H catalyst (23 mg) was added and the mixture was heated to 100 °C for an appropriate time (Products **3a-c**, **3e** stirred for 60 minutes; **3d** stirred for 30 minutes at RT; **3f** and **3g** stirred for 40 minutes). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Then chloroform (1 × 5 mL) was added to the reaction mixture and the catalyst was separated using an external magnet. The chloroform layer was separated, evaporated under reduced pressure. The crude mixture purified under silica gel column chromatography (Ethyl acetate and hexane 1:4).

Supplementary Material

Detailed experimental procedures and NMR spectras are available as supplementary material.