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

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ABSTRACT

Fe_3O_4-OSO_3H was identified as an efficient reusable catalyst for the facile synthesis of diarylmethyl indole derivatives under neat condition by C–C bond forming reaction. Fe_3O_4-OSO_3H catalysis was further extended to C–N bond forming reactions and for the synthesis of spermicidal 3,3′-di(indolyl)oxindole derivative. All the products were obtained in good to excellent yields.

Introduction

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 anti-viral,[3] anti-HIV,[4] anti-cancer,[5] antiproliferative,[6] antibacterial,[7] cytotoxic,[8] antitubercular[9] and anti-inflammatory 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] Ugi[16] and for the synthesis of chromenes, pyrimidines and epoxide derivatives.[17–19] Recently, Firouzabadi and co-workers reported functionalized Fe_3O_4 catalysed bis(indolyl)methane synthesis (Scheme 1).[20]

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 perfluorooctanesulfonate[23] and $FeCl_3$[24] 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 Fe_3O_4 catalysed diarylmethyl indole synthesis in an environmentally benign medium is worth investigating.

Results and discussion

Magnetic Fe_3O_4 nanoparticles were prepared through aqueous co-precipitation method[25] and are characterized by powder XRD technique (see electronic supporting information). Fe_3O_4 (10 mol%) catalysed 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 improve the reaction outcome. The poor product yield could be attributed to the mild acidic nature of Fe_3O_4 nanoparticles.

It was previously reported in the literature that sulfonic acid derivatives are good catalysts for the substituted indole derivative synthesis.[26] Replacement of Fe_3O_4 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%

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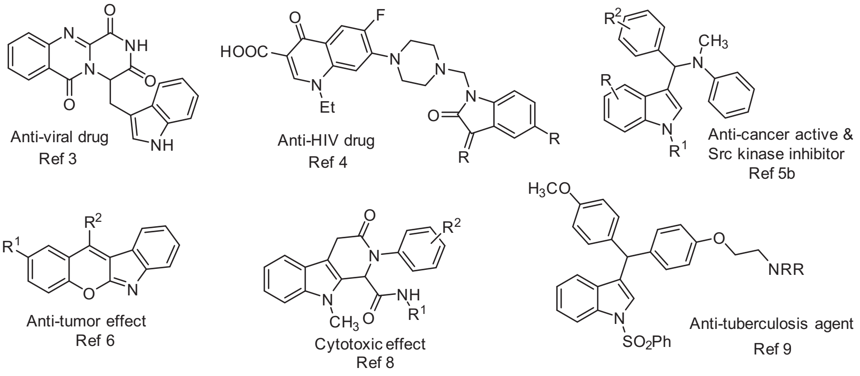
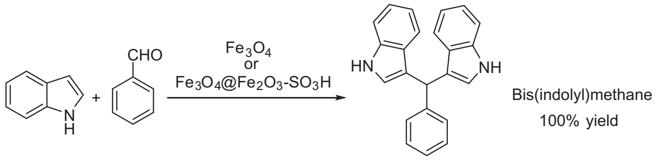
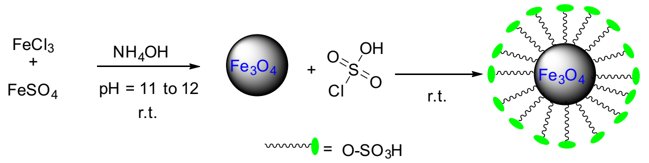


Figure 1. Representative examples of indole based bioactive skeletons.



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

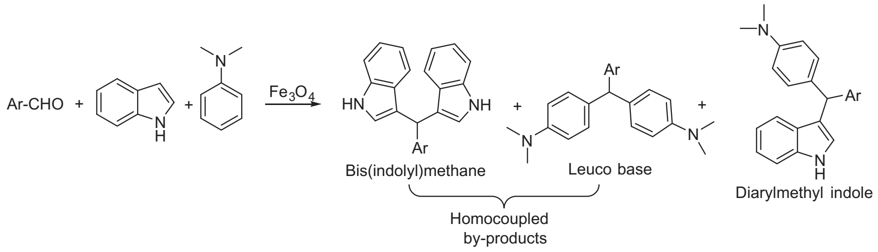


Scheme 4. Synthesis of sulfonic acid functionalized Fe_3O_4.

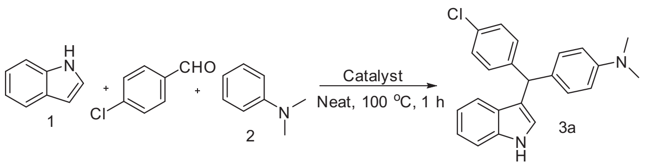
along with the formation of 28% of bis(indolyl)methane by-product (Scheme 3). Though the later result is encouraging, chlorosulfonic acid is corrosive, hygroscopic and lachrymatory in nature. Moreover, it reacts violently with water to form HCl and H_2SO_4. Hence, we have decided to synthesize and investigate the catalytic potential of sulfonic acid anchored Fe_3O_4 nanoparticles (Fe_3O_4-OSO_3H). Fe_3O_4-OSO_3H was synthesised by closely following a literature procedure and the product was obtained as fine brown powder (Scheme 4).[27]

The formation of sulfonic acid embedded Fe_3O_4 was confirmed by comparing the IR spectrum of Fe_3O_4 before and after functionalization (Fig. 2A and 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 (Fig. 2B). SEM analysis of the Fe_3O_4-OSO_3H showed the materials are of ~23 nm dimension (Fig. 2C and D). The clustering nature of Fe_3O_4-OSO_3H 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 1 M NaCl (pH 6.32), 100 mg of Fe_3O_4-OSO_3H was added and stirred for 2 h. 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}.

Fe_3O_4-OSO_3H catalyzed synthesis of **3a** in non-polar (toluene), polar aprotic (CH_3CN) and polar protic (H_2O) 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-OSO_3H (23 mg) efficiently catalysed one-pot synthesis of diarylmethyl indole **3a** in 88% yield (Scheme 5, Table 1, entry 6). Recyclability of the Fe_3O_4-OSO_3H 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



Scheme 2. Fe_3O_4 catalysed diarylmethyl indole synthesis.



Catalyst	Yield(%)
Fe_3O_4	34
p-$CH_3C_6H_4SO_3H$	37
$ClSO_3H$	48

Scheme 3. Fe_3O_4 and sulfonic acid catalysed diarylmethyl indole synthesis.