



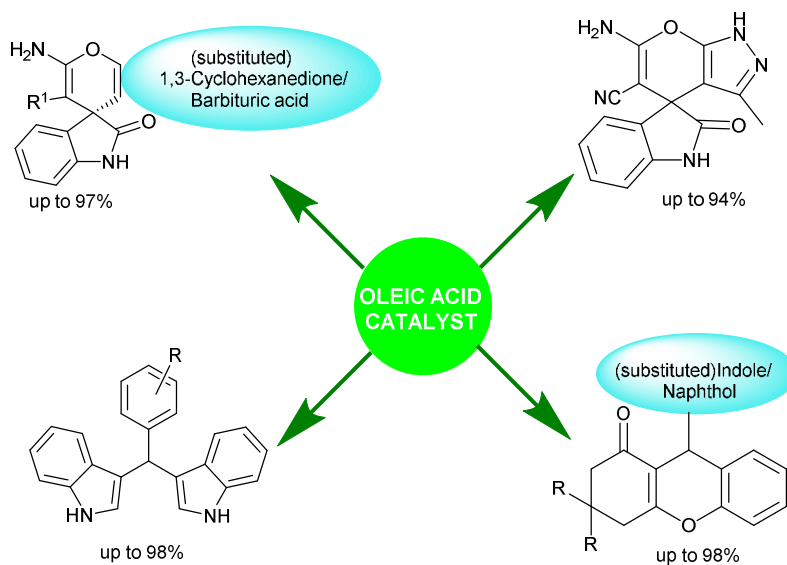
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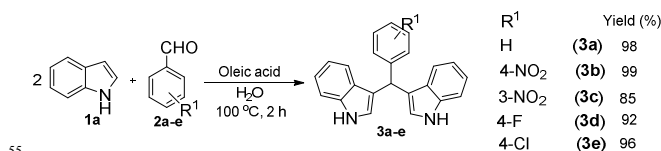
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Oleic acid was identified to catalyse bis(indolyl)methane and densely functionalized 4*H*-chromene, spirooxindole and spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives synthesis in good to excellent yield. Synergy between Brønsted acidity and surfactant ability of naturally available oleic acid was exploited to carryout aforementioned transformations.

Indole and its derivatives are widely abundant in natural products and bioactive skeletons.¹ Indole derivatives were used as novel efflux pump inhibitors,² neuroprotective agents,³ fluoride ion sensors,⁴ cox-2 inhibitors⁵ and promising anti-cancer agents.¹ Similarly, spirooxindole and chromene derivatives are present in vast array of biologically significant molecules.⁶⁻¹¹ Mitraphylline is a representative example of spirooxindole molecule with excellent anticancer activity against neuroblastoma cell line.¹² Though several catalysts are available for such molecules synthesis,¹³⁻¹⁵ many of them have notable disadvantages such as limited substrate scope, high cost, toxicity, difficulty in catalyst preparation etc. Hence, identification of a robust, readily available, non-toxic catalyst that yield library of 3-substituted indole skeletons in an environmentally benign solvent is always attractive. Unlike surfactants, fatty acids are lesser explored as catalyst primarily due to their mild Brønsted acidity and poor solubility in water. Kobayashi and co-workers reported decanoic acid catalysed 3-substituted indole synthesis.^{16a} Mase et al., showed that the presence of fatty acid reduce the catalyst loading and improved the product yield in organocatalytic direct aldol reaction.^{16b} Reports on Brønsted acid catalysed synthesis of 4*H*-chromenes and spirooxindole derivatives are limited to dodecyl benzenesulfonic acid, gluconic acid and proline.¹⁷ To the best of our knowledge, unmodified oleic acid catalysed substituted indole derivative synthesis hasn't been reported.

During the investigation on "oleic acid functionalized iron oxide" catalyzed bis(indolyl)methane synthesis, we have identified the excellent catalytic potential unmodified oleic acid itself. Oleic acid and other C-18 fatty acid counterparts are diversely distributed in plant oils.^{18a} Oleic acid being scarcely soluble in water (~0.1 mmol/l)^{18b} has a commendable catalytic ability to promote the reaction (Table 1, entry 3). Furthermore, isolation of the products from the reaction mixture was done by simple filtration. Reactions carried out in oleic acid soluble solvents such as ethanol and acetonitrile did not yield the corresponding

bis(indolyl)methane **3a** (Table 1, entry 6,7). For the reactions carried out in water, Breslow hydrophobic effect, hydrogen-bonding and polarity effects greatly assist the easy formation of products.¹⁹ Oleic acid mediated bis(indolyl)methane synthesis was found to be general for various substituted aldehydes (Scheme 1).



Scheme 1 Oleic Acid catalysed bis(indolyl)methane synthesis

Table 1 Reaction condition optimization for **3a** synthesis

Entry	Catalyst (mol%)	Solvent	Time (h)/ (Temp °C)	Yield (%) ^a
1	OA(12.5) ^b	H ₂ O	2(RT)	Trace
2	OA(12.5)	H ₂ O	10(RT)	84
3 ^c	OA(12.5)	H ₂ O	2(100)	98 ^d
4	OA(5.0)	H ₂ O	2(100)	65
5	OA(12.5)	H ₂ O	1(100)	96
6	OA(12.5)	C ₂ H ₅ OH	2(100)	Trace
7	OA(12.5)	CH ₃ CN	2(100)	Trace

^aYields are for the isolated products. ^bOA is oleic acid. ^cIn the absence of oleic acid, product was formed in 56% yield. ^dReaction performed with 20 mol% catalyst also gave 98% yield in 2 h.

Reaction carried out at room temperature increased the reaction completion time to 10 h (Table 1, entry 2). Catalyst loading of 12.5 mol% was necessary to achieve optimum yield (Table 1, entry 3 vs 4). Further increase in catalyst load to 20 mol% did not improve the reaction outcome (Table 1, foot note *d*). Addition of oleic acid and organic substrates in water resulted in the initial formation of two distinctly separate layers. The formation of white emulsion (oil-in-water type) during the course of reaction could be due to the formation of micelle or micelle-like colloidal aggregate.^{20a-b} Fig. 1 shows the light microscopic observation of colloidal dispersion of oleic acid and organic substrates in water. The high reaction rate of oleic acid catalysed reaction in water relative to organic solvents (Table 1, entry 3 vs 6,7) could be attributed to the high concentration of substrates inside the micelle-like spherical droplet formed by oleic acid on water. Each droplet may act as a hydrophobic reaction site that enables the

smooth transformation of substrate to the product.²¹

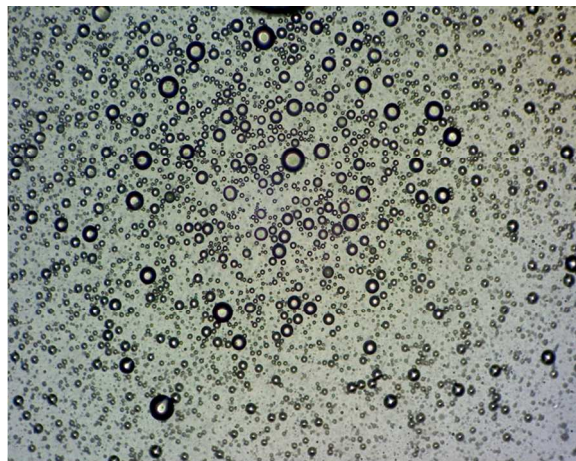
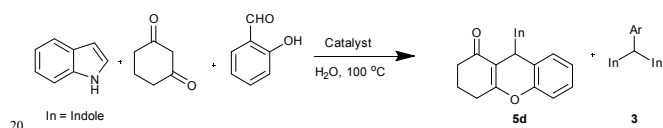


Fig. 1 Light microscopic image of oleic acid, indole and benzaldehyde in water.

Representative 4*H*-chromene synthesis was chosen as model reaction to evaluate the scope of oleic acid catalysis (Table 2). The synthesis of 4*H*-chromene is challenging due to the competitive formation of bis(indolyl)methane by-product **3**. It should be noted that bis(indolyl)methane formed even in the absence of catalysts (Table 1, Footnote *c*). Reaction with relatively stronger acids such as acetic acid resulted in the formation of bis(indolyl)methane by-product (Table 2, entry 2). Since saturated solid fatty acids (palmitic acid, stearic acid) failed to accommodate all lipophilic substrates readily, competitive uncatalyzed reaction yielded bis(indolyl)methane by-product along with product **5d** (Table 2, entry 4, 5).

Table 2 Screening of catalytic efficiency of 4*H*-chromene synthesis



Entry	Additive ^a	5d Yield (%) ^b
1	Benzoic acid	Trace
2	Acetic acid	Trace ^c
3	Caprylic acid	79
4	Palmitic acid	57 ^c
5	Stearic acid	43 ^c
6 ^d	Oleic acid	84 ^e
7	CTAB	87
8	Triton-X-100	Trace

^a12.5mol% of additives were used. ^bYields are for the isolated products. ^cFormation of bis(indolyl)methane observed. ^dIn the absence of catalyst only 29% of product is formed. ^eOleic acid was recyclable up to 4 cycles

Micelle-like environment provided by the liquid fatty acids (caprylic acid, oleic acid) readily incorporated hydrophobic substrates and resulted in facile formation of product (Table 2, entry 3, 6). Reaction carried out with cationic surfactant (CTAB) proved micellar environment favours product formation (Table 2, entry 7). It should be noted that CTAB is toxic to human skin cells (HaCaT keratinocyte) even in 10 μM concentration.²²

Interestingly, non-ionic surfactant didn't yield product **5d**. These studies revealed that the both Brønsted acidity and surfactant nature of oleic acid was utilized in the synthesis of **5d**. Studies on recyclability of oleic acid revealed that the catalyst retain its activity till four cycles (Table included in ESI). Wider substrate scope, ready availability, non-toxic nature, recyclability put oleic acid distinctly ahead of the rest of the screened catalysts. Oleic acid catalysed 4*H*-chromene synthesis was found to be general for various nucleophiles such as β-naphthol, *N*-methylindole and 6-methoxyindole (Figure 3). The structure of a representative 4*H*-chromene product **5e** was further confirmed unequivocally by single crystal XRD studies (Figure 2).²³

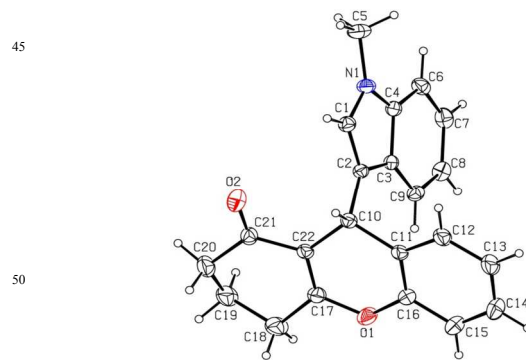
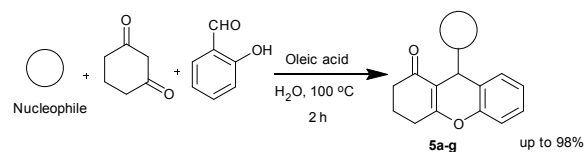


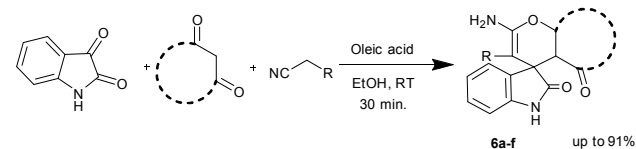
Fig. 2 Crystal structure of product **5e**. Ellipsoids are drawn at the 20% probability level and H atoms are shown as small spheres of arbitrary radius

Unlike 4*H*-chromenes and bis(indolyl)methanes, spirooxindoles **6** synthesis carried out in water solvent failed to yield the product in good yield. This could be due to the high solubility of malononitrile in water which restrict the free passage of malononitrile to the micelle-like hydrophobic pocket formed by the oleic acid. Reaction performed in amicable polar protic solvent such as ethanol provided spirooxindole **6a** in 91% yield within 30 minutes (Images of sequence of addition was given in ESI). The high reaction rate could be attributed to the presence of highly reactive malononitrile in the reaction medium. Apart from barbituric acid, dimedone, 1,3-cyclohexandione, *N*-methylbarbituric acid, thiobarbituric acids also gave spirooxindole in good yield (Scheme 2, Figure 3).

4*H*-Chromene synthesis



Spirooxindoles synthesis



Scheme 2 Oleic Acid catalysed 4*H*-chromenes and spirooxindole synthesis

At this juncture, the precise mechanism by which oleic acid catalyse the reaction is unclear. The success of the oleic acid

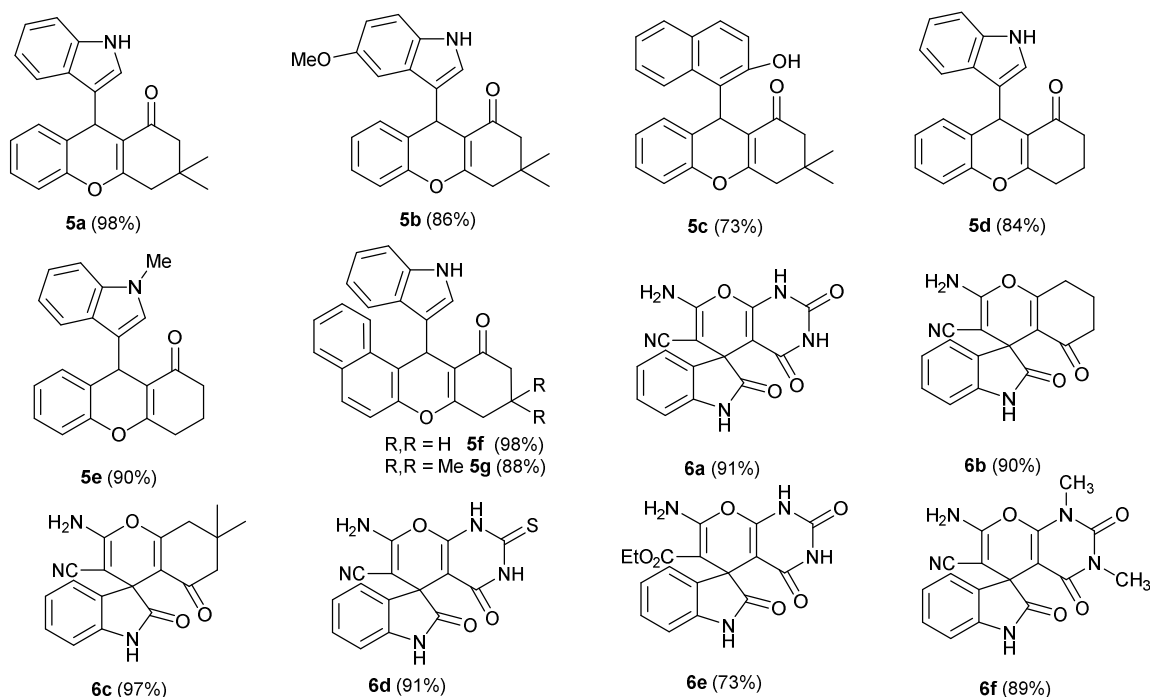
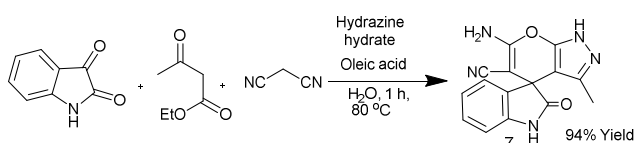


Fig. 3 Synthesized 4H-chromene and spirooxindole derivatives

5 catalysis in bis(indolyl)methane and substituted indole synthesis could be attributed to the inherent Brønsted acid-surfactant-combined catalytic effect. Out of interest we have further extended the scope of oleic acid catalysis to the spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] **7** synthesis by the four-component reaction of isatin, hydrazine hydrate, ethyl acetoacetate and malononitrile in water. To our delight the expected product **7** was formed in 94% yield (Scheme 3).



Scheme 3 Oleic Acid catalysed pyrazole synthesis

15 Conclusions

In conclusions, biodegradable, non-toxic, naturally available oleic acid was identified to catalyze substituted indole derivatives synthesis. The reaction was found to be general and hence the scope of the reaction is very high.

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Notes and references

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