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Extending the scope of oleic acid catalysis in diversity-oriented synthesis of chromene and pyrimidine based scaffolds†

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Readily available, non-toxic, biodegradable oleic acid was found to catalyse 4*H*-chromene derivatives syntheses in good yields in a water medium. A facile domino one-pot protocol was also developed for the oleic acid catalysed pyrimidine-fused heterocycle synthesis by pseudo three-component, three-component and four-component reactions. All the products were obtained in good to excellent yields. Oleic acid catalysis was further extended to the synthesis of curcumin based bioactive molecules.

1. Introduction

Diversity-oriented synthesis offers a unique way to synthesize structurally diverse molecular scaffolds and bioactive skeletons by varying substrate functionalities and molecular building blocks.[1] Hence, diversity-oriented synthesis carried out with readily available environmentally benign solvents and reagents is attractive. Water is a readily available, non-toxic, inexpensive, and environmentally benign solvent which facilitates easy isolation of products from the reaction medium by simple filtration.[2] Oleic acid is a naturally derived monounsaturated liquid fatty acid distributed in plant oils.[3] Until now, applications of oleic acid are largely confined to biodiesel production, dietary and medicinal applications.[4] Despite having lengthy lipophilic alkyl chain and hydrophilic carboxylic acid head group, oleic acid catalysis in water largely remains unexplored due to its poor solubility in water. However, oleic acid forms stable emulsion in water under sonication conditions.[5] Recently, we have reported unmodified oleic acid catalysed synthesis of substituted chromene derivatives in water medium.[6]

Chromene and their derivatives are widely sought for their extensive use as bioactive molecules and as photochromic materials.[7] Likewise, pyrimidine-fused heterocyclic derivatives are ubiquitous in several bioactive skeletons.[8,9] Representative example of bioactive chromene and pyrimidine-fused heterocyclic derivatives are presented in Fig. 1.[10–15] Insertion of indole moiety to a heterocyclic core could enhance the desirable biological properties of the parent core molecule. For example, introduction of indole moiety to 4*H*-chromene skeleton improved the apoptosis potency of 4*H*-chromene derivatives to nanomolar concentration.[15]

Synthesis of indole tethered 4*H*-chromenes can be achieved by the iodine catalysed Michael addition–intramolecular cyclization reaction or by indium chloride catalysed multicomponent reactions.[16] The former method require refluxing the reactants in toluene solvent and the later method use expensive catalyst. Apart from these methods, catalysts such as nano Bi_2WO_6,[17] polystyrene supported sulfonic acid,[18] amberlite resin,[19] $Ba(OTf)_2$,[20] trifluoroethanol[21] and ionic liquids[22] are reported for the 4*H*-chromene skeleton synthesis. Many of the reported catalysts have notable disadvantages such as tedious procedures for catalyst preparation, limited substrate scope, excess use of organic solvents and non-biodegradability of

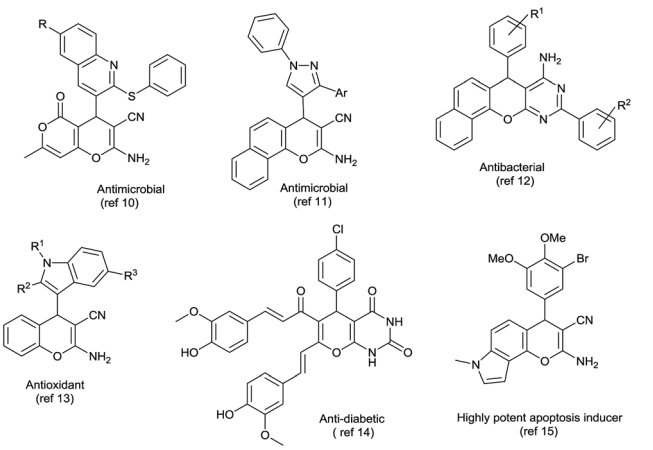

Fig. 1 Bioactive 4*H*-chromene and pyrimidine-fused heterocycles.

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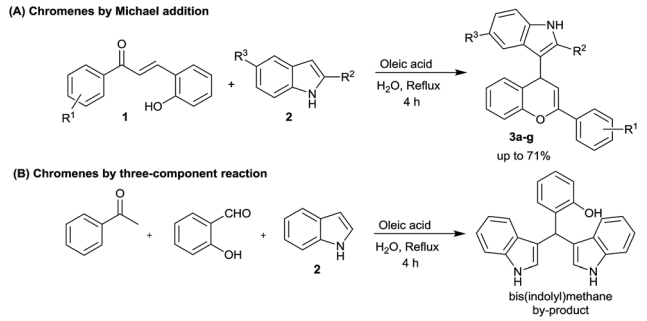
catalyst. Hence, it is of interest to investigate the catalytic potential of oleic acid in indole tethered 4*H*-chromenes synthesis and further extend oleic acid catalysis to pyrimidine-fused heterocycles synthesis.

2. Results and discussion

2.1 Oleic acid catalysed 4*H*-chromene synthesis

Addition of lipophilic oleic acid to water forms oil-in-water type emulsion in water (ESI†). Oleic acid catalyzed reaction of 2-hydroxychalcone derivative **1** and indole **2** on water gave the corresponding 4*H*-chromene products **3a–g** in good yields by the Michael addition followed by intramolecular cyclization reaction (Scheme 1A). Unlike previous methods,[16] in the present study intramolecular dehydration takes place in water medium.



Scheme 1 Oleic acid catalysed 4*H*-chromene synthesis.

At room temperature formation of product **3** was not observed. Oleic acid catalysed 4*H*-chromene synthesis was found to be general for various substituted 2-hydroxychalcone derivatives (Fig. 2). Attempts to carry out one-pot synthesis of 4*H*-chromene **3a** by the reaction of acetophenone, salicylaldehyde and indole were not successful (Scheme 1B). The high nucleophilicity of indole towards aldehyde group resulted in the facile formation of bis(indolyl)methane by-product.[23]

To circumvent the formation of bis(indolyl)methane by-product, acetophenone in Scheme 1B was replaced with highly reactive malononitrile. To our delight, oleic acid catalysed three-component reaction gave the corresponding indole tethered 4*H*-chromene derivatives **3h–n** at room temperature itself (Scheme 2). It was previously reported in the literature that malononitrile readily reacts with salicylaldehyde to form iminochromene type of products.[24] We presume the facile formation of iminochromene in the reaction medium followed by the nucleophilic addition of indole to iminochromene **5** paved way for the formation of desired product **3h** at room temperature itself. Generality of oleic acid catalysis was screened with *N*-methylpyrrole and various substituted indole derivatives and all the 4*H*-chromene derivatives were obtained in good yields (Fig. 2).

To precisely understand the efficiency of oleic acid catalysis, we have screened the representative 4*H*-chromene **3h** synthesis with various Brønsted acids and surfactants (Table 1). Since **3h** synthesis was carried out at room temperature, role of thermal effect to drive the reaction can be nullified. Reaction of salicylaldehyde and malononitrile may result in the immediate

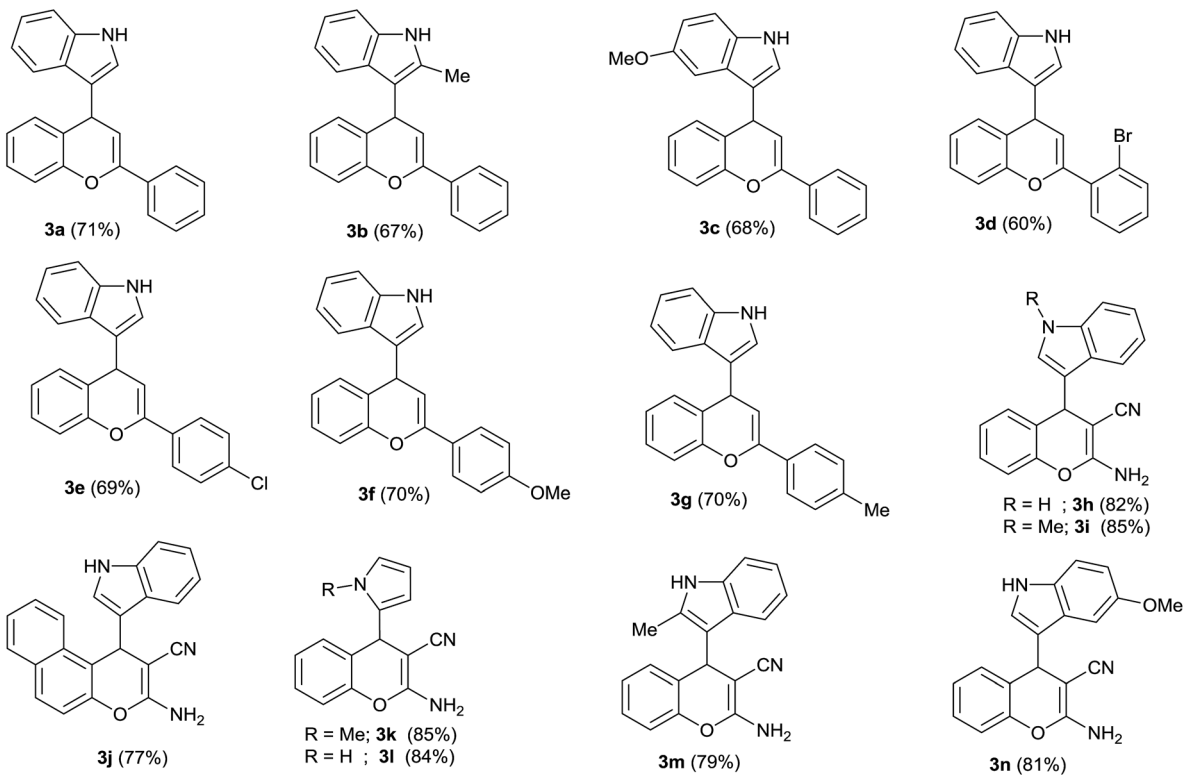
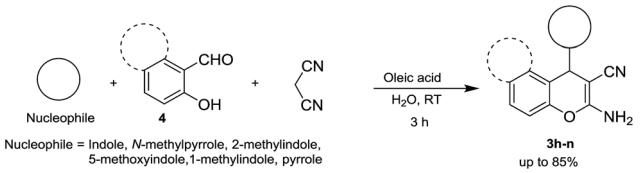
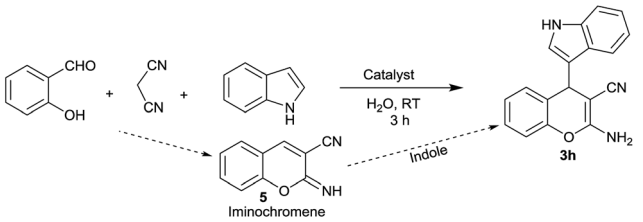


Fig. 2 Synthesized 4*H*-chromene derivatives.



Scheme 2 Oleic acid catalysed 4*H*-chromene synthesis by three-component reaction.

Table 1 Screening of reaction condition for **3h** synthesis[a]



Entry	Catalysts (12.5 mol%)	Yield[b] (%)
1	—	Trace
2	Acetic acid	28
3	Isonicotinic acid	NR
4	Caprylic acid	73
5	Capric acid	75
6	Myristic acid	61
7	Oleic acid	82
8	SDS[c]	Trace
9	CTAB[d]	59

[a] All the reactions were carried out with 1 mmol of salicylaldehyde, 1 mmol of malononitrile and 1 mmol of indole in 3 mL of water. [b] Yields are for the isolated products. [c] Sodium dodecyl sulfate. [d] Cetyltrimethylammonium bromide.

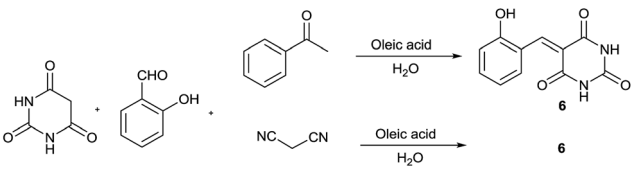
formation of iminochromene **5** derivatives (Table 1).[25] The poor solubility of iminochromene in water resulted in the formation of heterogeneous reaction mixture. The protonation of imine moiety by the Brønsted acid followed by the Michael addition of indole could have resulted in the formation of product **3h**. Brønsted acids such as acetic acid and isonicotinic acid without having lengthy lipophilic alkyl chain were inefficient to accommodate the hydrophobic iminochromene **5** and indole. It could be one of the reasons for the poor formation of product **3h** with aforementioned acids (Table 1, entry 2 and 3). Lipophilic fatty acids such as caprylic acid (C-8), capric acid (C-10), myristic acid (C-14) and oleic acid (C-18) gave the chromene product **3h** in good to excellent yields (Table 1, entries 4–7). The cationic surfactant gave relatively better yield than the anionic surfactant (Table 1, entry 9 *vs.* 8).

Kobayashi *et al.*, reported that dodecylbenzene sulfonic acid, a surfactant type Brønsted acid forms stable colloidal particles in presence of organic substrates in water and asserted that colloidal dispersion plays a seminal role in determining the rate of Mannich-type reaction in water.[26] Akin to that, oleic acid, a naturally available, biodegradable Brønsted acid also forms stable colloidal dispersion in presence of substrates (ESI†). We presume formation of lipophilic colloidal dispersion may act as suitable reaction medium for hydrophobic substrates and thereby facilitate the smooth formation of 4*H*-chromene derivatives.

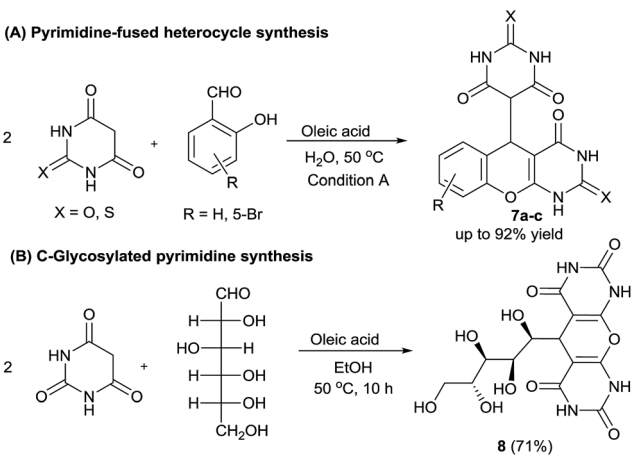
2.2 Oleic acid catalysed pyrimidine-fused heterocycle synthesis

It is of interest to extend the oleic acid catalysis to pyrimidine-fused heterocycle derivatives synthesis. Previously reported pyrimidine-fused heterocycle synthesis requires sophisticated sonication[27] or microwave[28] techniques or use of catalysts such as diammonium hydrogen phosphate,[29] DABCO,[30] *p*-toluenesulfonic acid[14] *etc.* Hence, it is of interest to investigate naturally derived oleic acid catalysed pyrimidine-fused heterocycle synthesis under conventional heating conditions in environmentally benign water or ethanol medium.

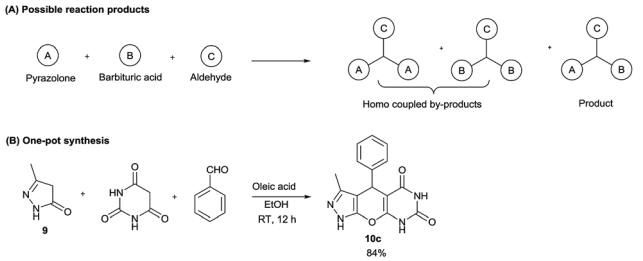
Three-component reaction of salicylaldehyde, barbituric acid, and acetophenone in water solvent at room temperature only resulted in the formation of Knoevenagel condensation product **6** (Scheme 3). The high acidity of barbituric acid (pK_a = 4.01)[31a] compared to acetophenone (pK_a = 15.8)[31b] resulted in the preferential nucleophilic attack of barbituric acid on salicylaldehyde carbonyl group leading to the formation of sparingly soluble Knoevenagel condensation product **6**. Under the reaction conditions, Michael addition of acetophenone onto **6** was not observed even at reflux conditions. Similarly, three-component reaction of salicylaldehyde, barbituric acid, and malononitrile in water at room temperature also gave the



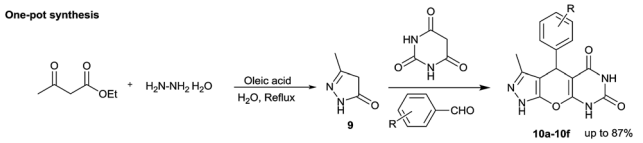
Scheme 3 Oleic acid catalysed pyrimidine-fused heterocycles synthesis.



Scheme 4 Pseudo three-component synthesis of pyrimidine-fused heterocycles.



Scheme 5 One-pot synthesis of pyrazolopyranopyrimidine derivatives.



Scheme 6 One-pot synthesis of pyrazolopyranopyrimidines by four-component reaction.

Knoevenagel condensation product **6** due to the relatively lower acidity of malononitrile ($pK_a = 11.1$)[31a] compared to barbituric acid. Attempts to prepare pyrimidine tethered heterocycles by the nucleophilic addition of barbituric acid to iminochromene **5** or 2-hydroxychalcone derivative **1** were not successful.

Akin to three-component reaction given in Scheme 3, oleic acid catalysed pseudo three-component reaction of barbituric acid (2 equiv.) and salicylaldehyde (1 equiv.) in water at room temperature also stopped at the Knoevenagel condensation stage itself due to the poor solubility of product **6** in water. The yield of the product was boosted to 92% by slightly increasing the reaction temperature to 50 °C (Scheme 4A, condition A). Conversely, the desired outcome of the reaction can be attained under room temperature itself by performing the reaction in ethanol solvent for 12 h (82% yield) or under reflux condition for 3 h (88% yield; condition B). Since condition A yielded the pyrimidine-fused heterocyclic products in good yield in water solvent, the rest of the derivatives **7a–c** were also prepared by following the same condition in good yields (Scheme 4A). Thus, a facile, one-pot, domino protocol was developed for the oleic acid catalysed pyrimidine-fused heterocycle synthesis in water medium.

It was surmised that replacement of salicylaldehyde with a monosaccharide in Scheme 4A would lead to the formation of C-glycosylated pyrimidine-fused heterocycles (Scheme 4B). Preliminary investigation on C-glycosylation reaction of barbituric acid (2 mmol) with unprotected D-glucose (1 mmol) in water medium was not successful due to the difficulty in isolation of hydrophilic product **8** from the aqueous medium. The reaction carried out in ethanol medium at 50 °C gave the corresponding product **8** in 71% yield (Scheme 4B).

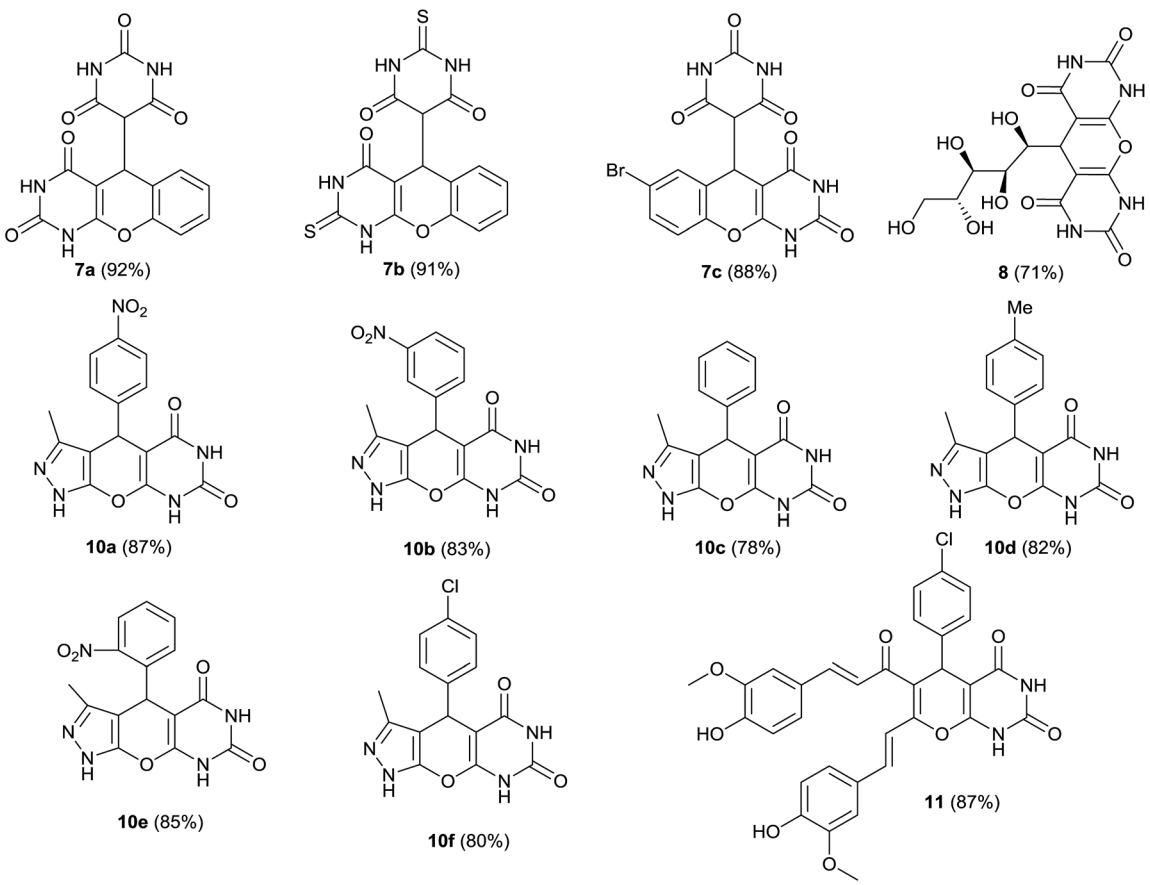


Fig. 3 Oleic acid catalysed pyrimidine-fused heterocycles synthesis.

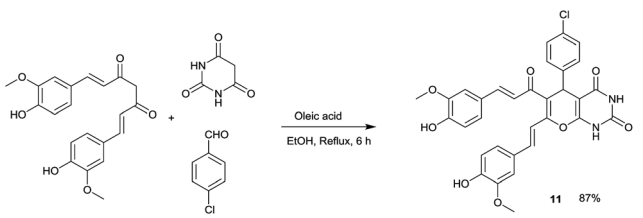
The scope of oleic acid catalysis was further extended to unsymmetrically substituted pyrimidine derivatives synthesis by performing three-component reaction. The synthesis of unsymmetrically substituted pyrimidine derivatives with two different heterocyclic core is difficult due to the competitive formation of homo coupled by-products (Scheme 5A).

The synthesis of **10c** carried out in water at room temperature failed to yield the desired product. The relatively high solubility of barbituric acid and pyrazolone in water could have reduced their reactivity towards sparingly soluble aldehyde. Interestingly, the reaction performed in ethanol solvent gave the product **10c** in 84% yield (Scheme 5B).

The scope of oleic acid catalysis was further extended to unsymmetrically substituted pyrimidine derivatives synthesis by four-component reaction since the construction of complex products from relatively smaller substrate scaffolds is always attractive (Scheme 6). Four-component reaction performed at room temperature in water or ethanol solvent did not yield the expected product **10**. Though three-component reaction was successful at room temperature (Scheme 5B), the requirement of elevated temperature is necessary for the *in situ* formation of pyrazolone **9** in Scheme 6.

The sequence of addition of substrates played a crucial role in determining the yield of the product. In presence of oleic acid, sequential addition of ethyl acetoacetate and hydrazine hydrate followed by the addition of barbituric acid and aldehyde after 15 minutes resulted in the formation of corresponding pyrazolopyranopyrimidine derivatives in good yields (Scheme 6). Conversely, combined addition of all substrates in one-pot at room temperature or elevated temperature didn't yield the expected product. The change in the course of the reaction could be due to the sequential *in situ* formation of pyrazolone **9** in the reaction medium which on further reaction with aldehyde and barbituric acid gave the product **10a–f** in good yield. The selectivity of the reaction is very high and the formation of homo coupled by-products was not observed in the reaction. The four-component reaction was found to be general for aldehydes with electron donating and electron withdrawing substituents gave the product in good yields (Fig. 3).

Recently, Khalafi-Nezhad and co-workers reported *p*-toluenesulfonic acid catalysed synthesis of anti-diabetic curcumin-based pyrano[2,3-*d*]pyrimidine derivatives and showed that these derivatives having good inhibitory activity against carbohydrate-hydrolysing α-amylase and α-glucosidase enzymes.[14] Oleic acid catalysis was applied to curcumin-based pyrano[2,3-*d*]pyrimidine derivative **11** synthesis and the product was obtained in 87% yield (Scheme 7).



Scheme 7 Oleic acid catalysed bioactive skeleton synthesis.

3. Conclusions

In conclusion, we have demonstrated the catalytic potential of naturally derived, biodegradable, unmodified oleic acid in the diversity oriented synthesis of chromene and pyrimidine derivatives in environmentally benign water or ethanol medium. Substrate scope of the oleic acid catalysis is very high and all the chromene and pyrimidine derivatives were obtained in good to excellent yields. Application of oleic acid catalysis was further extended to curcumin based bioactive skeleton synthesis.

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