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Graphical Abstract

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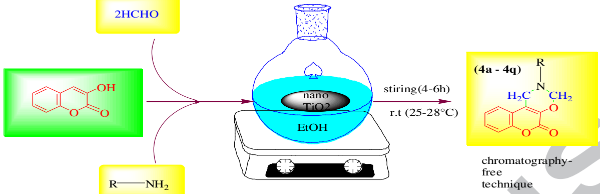

Four new bonds (one C-C, one C-O and two C-N) are formed in a single operation in this pseudo four-component reaction.

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ABSTRACT

An expeditious, one-pot, pseudo four-component coupling reaction between 3-hydroxy coumarin, formaldehyde and amine catalyzed by reusable TiO_2 nanopowder in ethanol at room temperature (25-28°C) under stirring condition to synthesize the chromeno[4,3-*e*][1,3]oxazine derivatives has been described. A wide range of substrate variation, environmentally benign reaction procedure, easy work-up, chromatography free synthesis, excellent yields with reusability of the catalyst make the methodology highly effective for the synthesis of chromeno[4,3-*e*][1,3]oxazine derivatives. To the best of our knowledge, this is the first report for the synthesis of chromeno[4,3-*e*][1,3]oxazines using 3-hydroxy coumarin.

In recent time, multicomponent reactions (MCRs) offer several opportunities in academia, industry, organic and medicinal chemistry for the generation of structural diversity, less toxic, eco-friendly and combinatorial libraries.[1] These one-pot, step economic reactions are highly efficient as they avoid time consuming, costly purification processes of the intermediates in addition to the protection and deprotection steps, formation of several bonds in a single step operation and manufacture of complex molecular architectures.[2] Coumarins present in various vegetables show immense biological activities like antibacterial, antifungal, antiviral, antitubercular, antimalarial, anticoagulant, anti-inflammatory, anticancer and antioxidant etc.[3] An increasing number of coumarin compounds have shown great potency in the treatment of various types of diseases.[4] In the present context, the chemistry of heterocyclic compounds have increased to a wide range and also are essential to comfort the human life. Most of the heterocyclic compounds which contain 1,3-oxazine moiety possess higher synthetic utility and act as useful intermediates for the variety of functional group interconversions.[4-6] This 1,3-oxazine ring system is also useful for the photo induced ring opening and thermal ring closing,[7] in addition to the synthesis of various type of drug sources that are reported.[8] The heterocyclic system of pyrano(chromeno)-[3,4-*e*][1,3]oxazine is promising both in terms of synthetic and biological aspects. Chromeno[3,4-*e*][1,3]oxazine type compounds are used as intermediates for the synthesis of a macrolide antitumor antibiotic lankacidin C.[9] A number of chromeno[3,4-*e*][1,3]oxazines exhibit high bactericidal and fungicidal actions.[10] Chromeno[3,4-*e*][1,3]oxazine derivatives are generally obtained by reactions of malonyl dichloride with amides, nitriles and heterocumulenes.[11] In addition, synthesis of chromeno[3,4-*e*][1,3]oxazine is performed by condensation of 4-hydroxycoumarins with azomethines and aldehydes.[12]

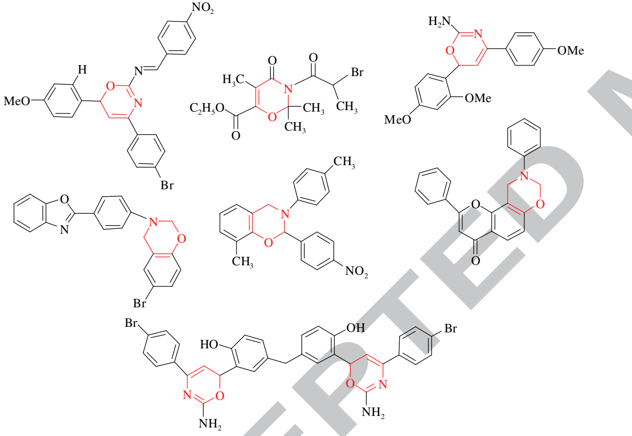
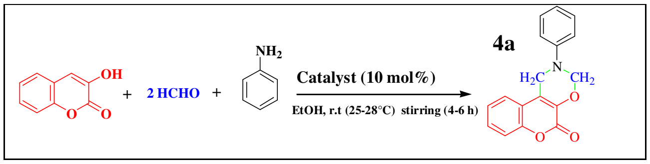


Figure 1: Some biologically important [1-3]oxazine derivatives.

In general, most of the above-mentioned reactions occur at higher energetic reaction condition with low product yield, longer reaction time and difficulties in work-up procedure. For such reasons, we must need to search a better alternative route to find a convenient and efficient method on the basis of green approach over the reported methods, for the synthesis of chromeno[4,3-*e*][1,3]oxazine derivatives. Another aspect towards the synthesis of these derivatives is the choice of a suitable catalyst. Recently, there is a consideration on the use and design of environmentally friendly heterogeneous catalysts to reduce the amount of toxic waste. Among them, nano scale metal oxides[13] have been efficiently used as catalysts for organic transformations.[14-17]The high reactivities of the nano catalyst depend on large surface areas or unusually reactive morphologies to a certain extent. Over the recent times, TiO_2 and nanosize-TiO_2 are being used as catalysts to promote the various type of organic reactions.[18-21] Therefore we consider the use of nano TiO_2 in the reaction due to the more efficiency and advantages of TiO_2 nano particle than other catalytic reagents. Thus, newer methodologies are still required for structural diversity and operational simplicity.

In this context, we present a new, one-pot, multicomponent methodology for the synthesis of chromeno-[4,3-e][1,3]-oxazine derivatives by the reaction of 3-hydroxycoumarin, formaldehyde and amines catalyzed by reusable TiO_2 nanopowder. As a prototype, the reaction of 3-hydroxycoumarin, formaldehyde and aniline (Scheme 1) was studied under different catalytic conditions summarized in Table 1. In our search of an efficient and environmentally benign catalyst, the preferred reaction was conducted in the presence of various catalyst at room temperature (25-28°C). At the beginning of investigation we considered several basic and acidic catalysts to set up a standard reaction condition. The experimental results showed that the reaction proceeds favourably under acidic conditions. After that various Lewis acids such as AcOH, H_3PO_4, $FeCl_3$ and TiO_2 nanopowder were examined in the reaction. The results indicated that in presence of TiO_2 nanopowder this reaction gives fair conversion and yield. In contrast to TiO_2 nanopowder, when the reaction switched to other catalysts the reaction offered very low yields (Table 1, entries 2-8) and conveniently, when the reaction was performed in the presence of 10 mol % of TiO_2 nanopowder at room temperature (25-28°C) for 6 h, the desired product **4a** was obtained with maximum yield (Table 1, entry 11). Although the reaction afforded the desired product even in presence of commercial TiO_2 (Table 1, entry 9), the isolated yield was comparatively lower than that with the synthesized TiO_2 nanopowder as the catalyst (Table 1, entry 10), Notably, in the absence of the catalysts only trace amount of the product was formed (matched by TLC) (Table 1, entry 1) after 15 h at room temperature, which could not be separated in pure form.

Table 1: Screening of catalysts for the multicomponent synthesis of chromeno-[4,3-e][1,3]oxazine derivatives*



Scheme 1

Entry	Catalyst(10 mol%)	Solvent	Isolated Yield (%)	Time (h)
1	-	EtOH	trace	15
2	AcOH	EtOH	55	10
3	Boric Acid	EtOH	49	10
4	4N HCl	EtOH	34	10
5	4N H_3PO_4	EtOH	24	10
6	$FeCl_3$	EtOH	53	10
7	SiO_2	EtOH	36	10
8	Al_2O_3 (acidic)	EtOH	48	10
9	CommercialTiO_2(10)	EtOH	82	10
10	TiO_2nanopowder(10)	EtOH	92	10
11	TiO_2nanopowder(10)	EtOH	92	6
12	TiO_2nanopowder(15)	EtOH	91	10
13	TiO_2nanopowder (5)	EtOH	88	10

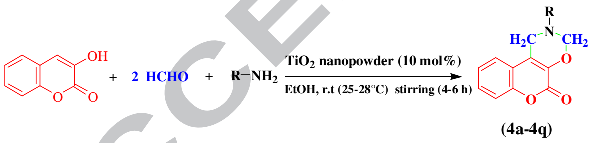
14	TiO_2nanopowder(10)	MeOH	55	6
15	TiO_2nanopowder(10)	ACN	65	6
16	TiO_2nanopowder(10)	DMF	50	6
17	TiO_2nanopowder(10)	DCM	40	6
18	TiO_2nanopowder(10)	THF	70	6

*3-hydroxy coumarin (1 mmol), formaldehyde (2.2 mmol), aniline (1 mmol) and 5 mL ethanol were taken in a 25 mL round bottomed flask. The resulting mixture was then stirred in the presence of catalysts for the specified times as shown.

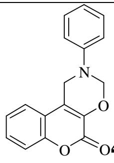
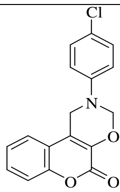
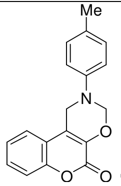
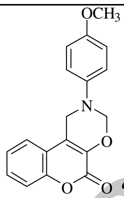
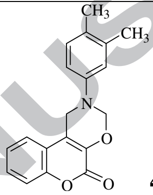
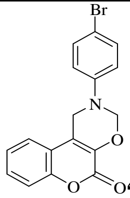
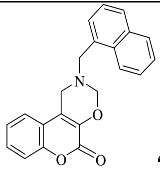
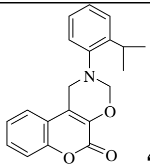
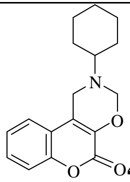
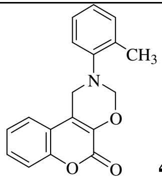
With these screening results in hand, we have investigated this pseudo four-component reaction in various solvents like MeOH, EtOH, ACN, DMF, DCM and THF. The best results were obtained at room temperature (25-28°C) by stirring the reaction mixture in EtOH with high yield of the product (Table 1, entry 10). Whereas other solvents presented very low yield compared to desired product (Table 1, entries 14-17). Although THF gave slightly higher yield but it was less than ethanol (Table 1, entry 18). Therefore in the presence of 10 mol % TiO_2 nanopowder, 3-hydroxycoumarin, formaldehyde and aniline (stoichiometric ratio 1:2.2:1) in ethanol were found to be the optimum conditions for the maximum yield of the reaction.

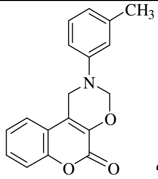
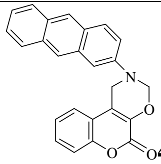
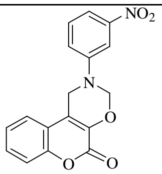
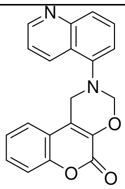
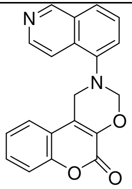
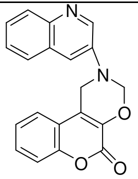
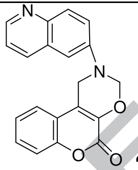
After the optimization of the reaction condition, we turned our focus to the substrate scope and generality of the reaction. A variety of amines were used (Table 2) under the optimized conditions. It was found that, when we introduced aromatic amines with electron-donating groups (like Me, OMe and isopropyl) (Table 2, entries 3, 4, 5 and 8) at different positions of the aromatic ring, it resulted in good to excellent yield of the desired product, whereas groups with electron-withdrawing nature (like Cl, Br and NO_2) (Table 2, entries 2, 6 and 13) gave slightly lower yield. Aliphatic amines like 1-aminomethyl naphthalene and cyclohexyl amine (Table 2, entries 7 and 9) also reacted well. Meanwhile, the substrate bearing a bulky polycyclic aromatic group like 2-amino anthracene (Table 2, entry 12) reacted well and gave the desired product **4l** in 76% yield. High product was also obtained when the reaction was performed with polycyclic hetero aromatic (Table 2, entries 14-17) amines.

Table 2: TiO_2 nanopowder catalyzed multicomponent synthesis of chromeno-oxazine derivatives.



Scheme 2

Entry	Product	Time(h)	Isolated Yield (%)
1	 **4a**	6	92
2	 **4b**	6	85
3	 **4c**	4	93
4	 **4d**	4	91
5	 **4e**	5	94
6	 **4f**	6	87
7	 **4g**	5	92
8	 **4h**	6	79
9	 **4i**	6	82
10	 **4j**	6	90

11	 **4k**	6	88
12	 **4l**	6	76
13	 **4m**	6	80
14	 **4n**	5	90
15	 **4o**	6	85
16	 **4p**	6	88
17	 **4q**	5	87

Additionally, we considered a standard reaction (Scheme 1) to investigate the catalytic recycle experiment (Table 3). The catalyst was easily recovered by the filtration throughout a sinter funnel after completion of the reaction (checking TLC). Then it was washed with EtOH for four times to remove any adhering organic compound. It was next dried under vacuum followed by drying in the oven completely. The catalyst (nano-TiO_2) was reused for the standard reaction for up to nine cycles without any appreciable loss of activity and after that we have observed a considerable amount of lowering of activity from 9th to 10th cycle.

Table 3: Recycling of the catalyst for the pseudo four-component coupling reaction of 3-hydroxycoumarin, formaldehyde and aniline (product **4a**)

Run	Time (h)	Yield (%) (isolated)
1	6	92
2	6	91
3	6	91
4	6	89
5	6	86
6	6	84
7	6	84
8	6	82
9	6	80
10	6	70

The catalyst TiO_2 nanopowder was synthesised by the previously reported standard gel combustion method[22]. The prepared catalyst was characterized by TEM, X-ray diffraction and BET surface area determination. The rutile structure of TiO_2 and characteristic peaks for the crystal planes (1 0 1), (0 0 4), (2 0 0), (1 0 5), (2 1 1), (2 0 4) (1 1 6), (2 2 0) and (2 1 5) are confirmed from X-ray diffraction, which are in agreement with the standard JCPDS value. The specific surface area of TiO_2 nanopowder was calculated $69.51 m^2 g^{-1}$ from nitrogen adsorption isotherm study. The pore size of the crystals was predicted by HR TEM analysis and all the above characterization data of TiO_2 is given in supplementary information.

Moreover, all the compounds were purified by simple recrystallization, even though the compounds were not subjected to chromatography. After filtering the catalyst (sintered funnel) from the reaction mixture, the solvent was pumped out by rotary evaporation. The crude product was then purified directly by recrystallization from ethyl alcohol-water mixture (5:1 v/v).

Structures of all the above synthesized chromeno[4,3-*e*][1,3]oxazines derivatives were fully characterized by ^1H and ^{13}C NMR and IR spectra. The final structure was confirmed by an X-ray crystallography study of a single crystal of the chromeno-[4,3-e][1,3]oxazine **4c** (Table 2, entry 3) which is given below in Figure 2.

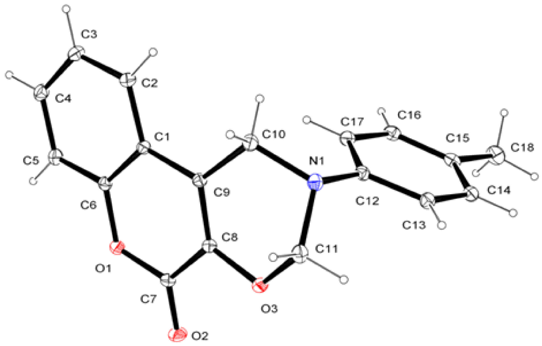
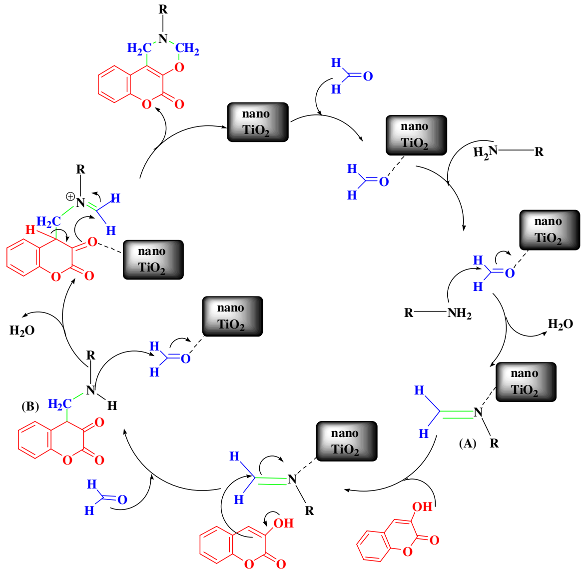


Figure 2: ORTEP plot of the chromeno-oxazine **4c** by the single crystal X-ray diffraction (Table 2, entry 3) (**CCDC 969794**)

A proposed mechanistic route for the formation of the products is exhibited in Scheme 3. At first, amination reaction occurs between the activated formaldehyde (by coordination with TiO_2 nanoparticle) and amine (RNH_2) followed by H_2O elimination provides imine intermediate “A” that is further activated by TiO_2. “A” is then attacked by 3-hydroxy coumarin to form “B**”** which further reacts with formaldehyde and eliminate H_2O. Next cyclization occurs to form the final product.

Activation of the formaldehyde through the weak interaction between the lone pair electron of oxygen and Lewis acidic sites (Ti^{4+}) on the surface of TiO_2 make it susceptible to nucleophilic attack by amine as well as 3-hydroxy coumarin. The step in which elimination of H_2O takes place is also facilitated by Ti^{4+}. The size of the TiO2 particles is more important for synthesizing the target product. The smaller size TiO_2 particles are more efficient for the reaction, because as the particles size decreases surface area for the contact of the reactants increases.



Scheme 3: A probable mechanistic pathway for the synthesis of chromeno-oxazine derivatives through recycling of TiO_2 nano particle.

In summary, we have described the utility of nanopowder TiO_2 in synthesizing the chromeno-oxazine derivatives in good to excellent yields. These are the first reported compounds in which two new C-N bonds, one C-O bond and one new C-C bond are formed in a single operation by the pseudo four-component coupling reaction. This study presents simple, efficient and one-pot multicomponent protocol, which provides several advantages such as short reaction times, high yields, easy working up, chromatography-free technique, catalyst recovery and reusability are other highlights of this work.

Supplementary data: The data of experimental details, catalyst TiO_2, characterization and spectroscopic report of all compounds along with 1H, 13C NMR and IR are given in the Supplementary section.

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1. Highly efficient multicomponent chromatography-free synthesis
2. Wide range of amines including aromatic, polyaromatic, alicyclic, aliphatic utilised
3. Catalyst reusability decreases the amount of toxic wastes in the environment
4. Green, environmentally benign methodology