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TiO₂ nano crystallites catalyzed water mediated microwave assisted regioselective three component domino Hydrolysis/Aldol/condensation/ Michael addition reaction-3-(1,5-dioxo-1,5-diphenylpentan-3-yl)quinolin-2(1H)-oneEethamukkala

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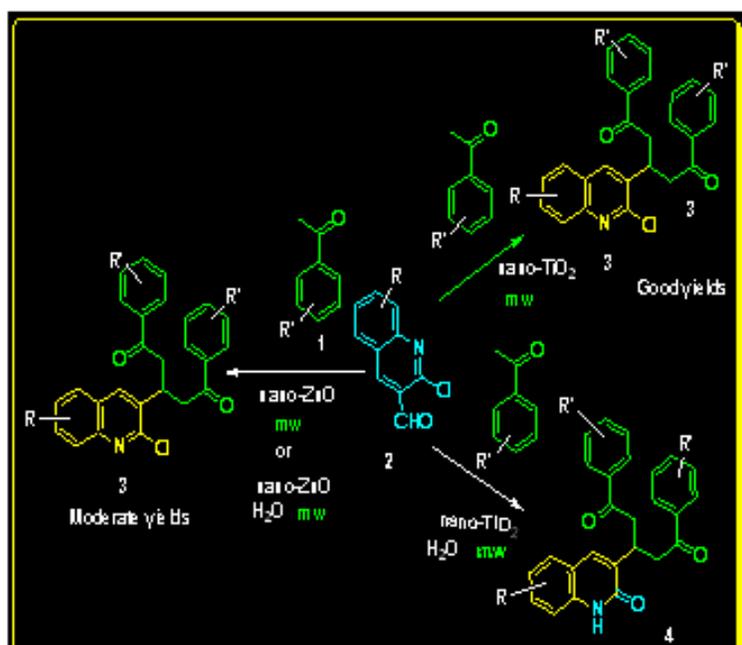
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ARTICLE

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A facile microwave supported, water intervened and nano crystalline TiO₂ catalyzed, synthesis of 1, 5-dicarbonyl derivatives, 3-(1,5-dioxo-1,5-diphenylpentan-3-yl)quinolin-2(1H)-ones is accounted for. This strategy utilizes the reversible water adsorption/de-sorption property of TiO₂ nano crystallites for the domino hydrolysis/Aldol/ condensation/Michael addition. The current methodology provided the coveted synthetic building blocks in an ecologically benevolent procedure including reusable catalyst, safe universal water medium, microwave support, multistep reaction in one-pot and the selectivity of the process.

Introduction

The 1,5-dicarbonyls and their analogues are significant synthetic intermediates that find their synthetic utility in pinacol coupling and in the establishment of pyridines, indenopyridines, benzoquinolines, substituted cyclohexanones, selenium, phosphorous containing heterocyclic and the poly-functional compounds. The dicarbonyls are possibly connected in coordination chemistry, molecular sensing and self-assembly devices.¹⁻⁷ Numerous methods have been created for the efficient synthesis of 1,5-dicarbonyl compounds involving C-C bond formation through Aldol-Michael addition,^{8, 9} conjugate addition of activated methylene compounds to α,β -unsaturated ketones,¹⁰⁻¹⁴ condensation of ketone enolate and the Mannich base.¹⁵ Gold and silver salts have even been utilized for electron withdrawing substrates that confined gold enolates and accomplished subsequent Michael reaction. Phenyl acetylene have in addition been applied rather than acetophenones¹⁶ and for the conjugate addition of the enones to Michael donor trimethylsilylenol ethers.¹⁷ The structuring of diketones from the aldehydes utilizing enol silyl ethers under PTC conditions in the presence of NaOH/TBAB is evidenced from the initially formed aldol product, which gets added to the enol silanes to form the desired diketones. Likewise, from enones and enol silyl ethers the C-C bond formation takes place through the conjugate addition in the presence of Lewis acid InCl₃ in water medium demonstrating efficient hydrous conditions.^{18, 19} Tandem cross coupling reaction (aldol reaction- β -elimination-Michael addition) of aryl methyl ketones with aromatic aldehydes has been exhibited by utilizing barium hydroxide /alkoxide catalyzed where enolates generated *in situ* in one-pot offered symmetrical 1,5-diketones in incredible yields.^{20,21} In the present scenario, organic synthetic methodology involving microwave irradiation has been emerging as furthermore promising

in correlation to the routine synthesis in the light of the fact to their numerous advantages including solvent-free condition, ambient pressure, enhanced reaction rate, clean, economical, simplicity of work-up and higher yields.²²⁻²⁸ Some of the restrictions in these reactions incorporate expensive reagents, alkaline alcohols or excess solvent, refluxing condition, reacting aldehydes must have electron withdrawing group. Additionally in the tandem reactions or others²⁹ there are conceivable outcomes of intramolecular aldol condensation of diketones to the cyclic product. Considering the above synthetic utility, downsides, it is fundamental to develop a proficient protocol that overcomes deficiencies of the reported strategies. In our proceeded with exploration interests in the synthesis of heterocyclics and C-C bond formations³⁰⁻⁴⁵ and focuses on the above contemplations, in the present study, TiO₂ nanoparticles have been investigated in the one-pot three component domino reactions in the synthesis of 1, 5 diketones containing quinoline ring systems under ambient and aqueous conditions.

The titanium dioxide (TiO₂) owing to their high surface area, uniform pore size, exceptional electronic and optical properties, has been employed in many fields, solar cells, lithium-ion batteries, sensors and catalyst supports and particularly in aqueous environment, including photo catalysis, gas sensing, etc.⁴⁶⁻⁵³ The adsorption of water is an intriguing field and structures an essential adsorbate in the TiO₂ surface that influences reaction processes. It is recently understood that water gets adsorbed either dissociatively or molecularly on the surface of the TiO₂ and is stabilized by intermolecular hydrogen bonding. The adsorption/desorption happens reversibly, where molecular water is the desorption product and the water molecule gets trapped inside the TiO₂ before re-combinative desorption in light of point defects in TiO₂, water leaves the surface on warming. The hydrophobic and hydrophilic TiO₂ respectively in the dark and UV exposure has been exploited for self

cleaning coating on mirrors and in antifogging⁵⁴⁻⁵⁷. With the above information in hand, the present study envisioned the exploitation of the adsorption/desorption behavior of dissociated or molecular water molecules in our proceeded with research interest toward green chemistry approach.

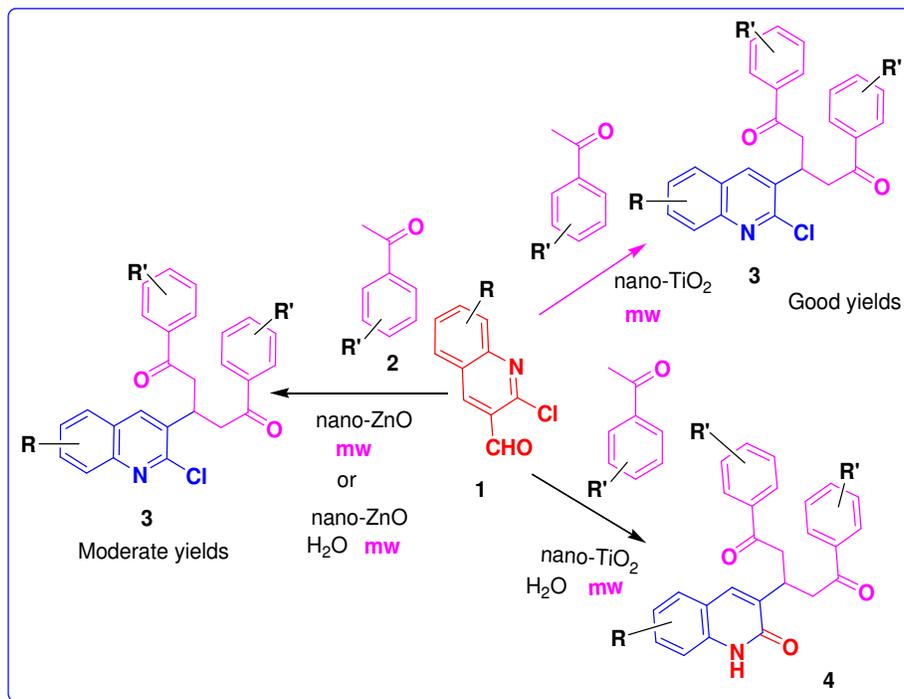
Result and discussions

Lately, tandem Knoevenagel/Michael addition reaction has been attempted by researchers under eco-friendly, environmentally benign solvent-free or safe aqueous conditions and microwave irradiation, with the expectation of staying away from long reaction time, tedious workup, undesirable side products and for accomplishing region-selective products, etc. As needs be, in the present study the TiO₂ nano crystallites have been examined in the synthesis of titled compounds (Scheme 1) by a clean, safe, high-yielding, inexpensive process and the reusability of the heterogeneous catalyst has likewise been investigated. To amplify the microwave effects, solid supports have been used. The experimental results reveal the TiO₂ under solvent free conditions provided the desired product, **3** (Scheme 1) and that the TiO₂ solid support under water medium, gave the quantitative yield of the desired product, **4** (Scheme 1). The utilization of water is a green synthetic approach that dodges an environmental pollution, and is an ideal solvent in organic synthesis. After completion of the reaction, by using suitable solvent, the product was dissolved and the insoluble solid support was separated, washed with the solvent, dried and was reused progressively for the least runs along these lines showing the reusability and recyclability of the catalysts.

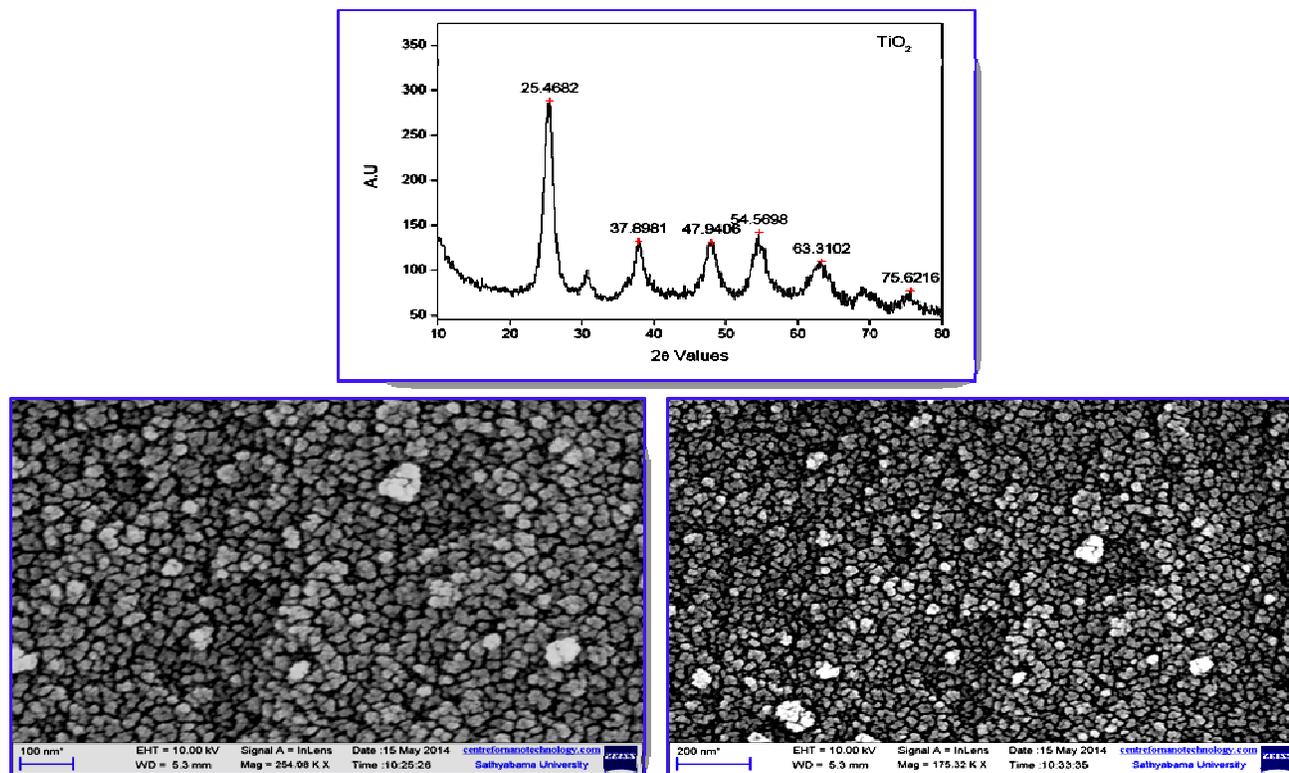
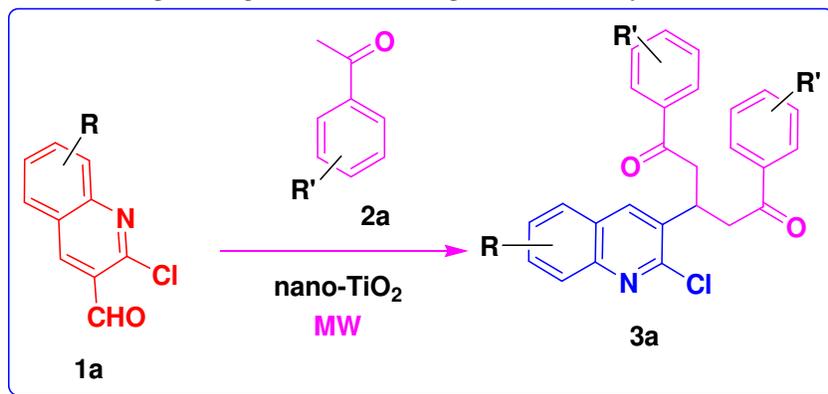
The titania nanoparticles needed for the present study was effectively obtained through a sol-gel process, employing titanium (IV) tetraisopropoxide (Ti[OCH(CH₃)₂]₄; TIP) precursor in ethanol.

To 34.5 mL ethanol, 0.1 mL of nitric acid was added drop by drop under vigorous magnetic stirring. Further, 16.91 mL TIP was gradually added with continued stirring for 10 min.; the obtained mixture was added drop wise to 150 mL of distilled water. The vigorous magnetic stirring was proceeded at room temperature for 30 minutes for gelation. The gels were then washed with distilled water, dried at 80 °C, ground well in mortar to acquire the nanocrystalline titania. The crystalline anatase phases were affirmed by X-ray diffraction studies that revealed XRD patterns at 2θ = 25.46° (101), 37.89° (004), 47.94° (200), 54.56° (105) and 63.12°. The scanning electron microscopy study revealed the crystalline, anatase titanium dioxide nanoparticles of 10-15nm (Figure 1).

A Preliminary study was carried out using a mixture of 2-chloro-3-formylquinoline **1a** (2mmol), acetophenone, **2a** (5 mmol) in 5mL ethanol under refluxed conditions in the presence or absence of commercial metal oxides including ZnO or TiO₂ catalysts and 1mg NaOH. The reaction did not proceed without NaOH to afford the desired diketone, **3a** (Scheme 2, Table 1 entry 1, 2 and 5) whereas traces of **3a** was formed in the presence of catalytic amount of ZnO or TiO₂ and 1mg NaOH as a base (Table 1 entry 4 and 6). The results revealed that both the catalysts and NaOH are essential for the reaction. Further, we varied the metal oxide, NaOH base loading from 2, 3 and 5 mg (Scheme 2, Table 1 entry 7-9). Amongst the investigated conditions, in the presence of 5 mg TiO₂, 1mg NaOH, the reaction offered the desired product, **3a** was acquired in a less yield of 37% (Scheme 2, Table 1 and entry 8). Notwithstanding, the ZnO likewise proceeded to offer the desired product in low yield of 20% after delayed reaction time (Scheme 2, Table 1 and entry 9). Comparative results were obtained under solvent free conditions. Supported by these result, a couple of optimization studies were carried out modifying the nano catalysts, catalyst loading, base loading, conventional or microwave heating under solvent free conditions.



Scheme 1. TiO₂ nanoparticles catalyzed synthesis of 1,5-diones

Fig 1 XRD pattern and SEM images of TiO₂ nanocrystallites

Scheme 2 Synthesis of 1,5-diones

Amongst the diverse catalysts screened, great yields were obtained using TiO₂ nanoparticles and the ZnO nanoparticles gave moderate yields under microwave conditions (Table 1, entries 10-14). Remarkably, the microwave irradiation studies showed that the use of 1mg NaOH is essential, and the reaction proceeded smoothly in the presence of 5mg TiO₂ to afford the desired product in high yields in comparison to the conventional approach (Table 1, entry 14). The microwave irradiation at 500W has been ended up being gainful amongst the tested 100, 200, 300, 500 and 800W (Table 1, entry 14).

The desired product, **3a** was affirmed by proton and carbon NMR, DEPT -135, 2D H-H, C-H COSY spectra, LCMS and HRMS information. To explore the scope of the tandem reaction under the optimized conditions, different, 2-chloro-3-formyl quinolines, **1a-g** and acetophenones, **2a-i** were investigated and the results are presented in the table 2. In any case, the reaction did not proceed with the cyclic and activated ketones, cyclohexanone, etc.

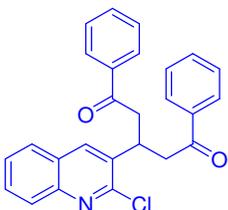
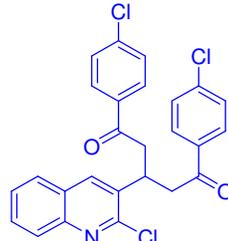
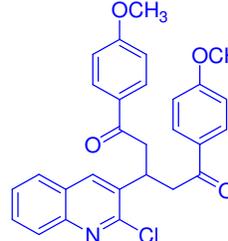
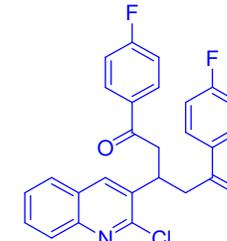
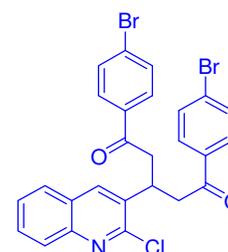
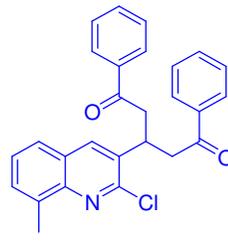
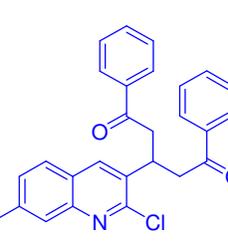
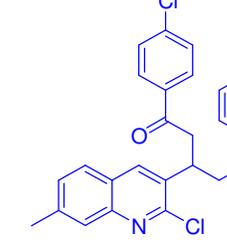
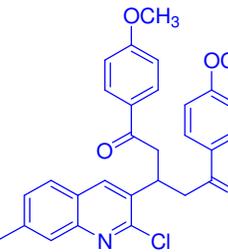
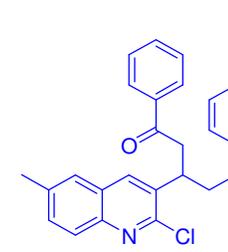
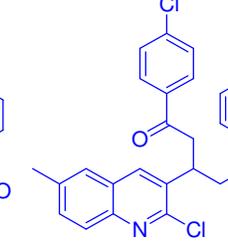
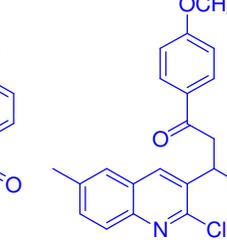
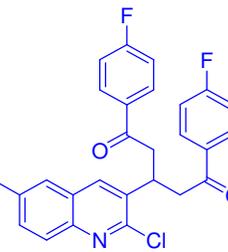
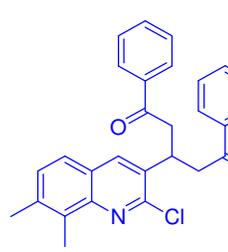
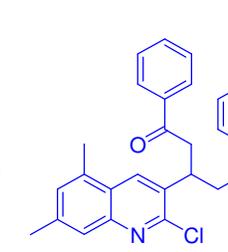
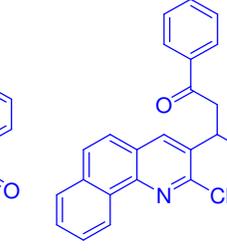
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Table 1 Selection of catalyst, catalyst loading, heating method^a

Entry	Catalyst		NaOH Base mg	3a % Yield	
	Metal oxide	Quantity mg		MW ^b	Con ^c
1	TiO ₂ or ZnO	0	0	NR ^d	NR
2	TiO ₂	1	0	NR	NR
3	TiO ₂ or ZnO	0	1	5	Trace
4	TiO ₂	1	1	18	Trace
5	ZnO	1	0	NR	NR
6	ZnO	1	1	10	Trace
7			2	20	
	TiO ₂	1	3	24	Trace
			5	27	
8		2	1	30	
	TiO ₂	3		33	Trace
		5		37	
9		2		11	Trace
	ZnO	3	1	16	
		5		20	
10	TiO ₂ nano	1	1	35	Trace
11		2		56	Trace
	TiO ₂ nano	3	1	60	
		5		84	
12	ZnO nano	1	1	20	Trace
13		2	1	24	Trace
	ZnO nano	3		30	
		5		40	
14	TiO ₂ nano	5	1	65, 78, 83, 84, 87 ^e	Trace

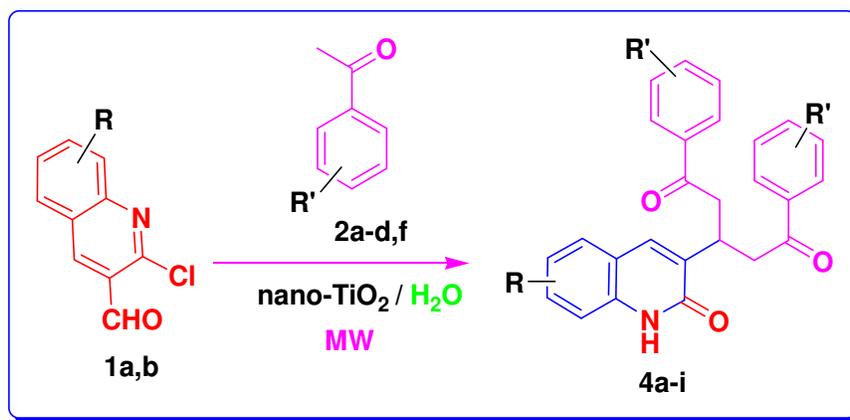
^a2-chloroquinoline-3-carboxaldehyde, **1a** (2 mmol), acetophenone, **2a** (5 mmol), ^bMicrowave irradiation at 500W, 13 min unless otherwise mentioned, ^cethanol reflux 2h, ^dNR-No reaction, ^eyields respectively for microwave irradiation at 100, 200, 300, 500 and 800 W.

Table 2: Microwave assisted synthesis of 1,5-diones^a

 3a, 13 min, 85 %	 3b, 15 min, 82 %	 3c, 11 min, 89 %	 3d, 10 min, 86 %
 3e, 20 min, 75 %	 3f, 15 min, 79 %	 3g, 14 min, 80 %	 3h, 16 min, 81 %
 3i, 12 min, 83 %	 3j, 15 min, 88 %	 3k, 16 min, 82 %	 3l, 10 min, 90 %
 3m, 11 min, 92 %	 3n, 18 min, 80 %	 3o, 15 min, 91 %	 3p, 19 min, 87 %

^a2-Chloroquinoline-3-carboxaldehydes, **1a-g** (2 mmol), acetophenones, **2a-i** (5 mmol), 1 mg of NaOH, 5 mg of TiO₂,

MW irradiation at 500 W.

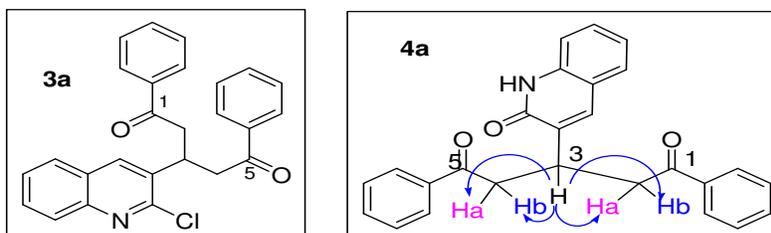


Scheme 3 Synthesis of oxo analogues of 1,5-diones

With these decently improved results in hand, the scope of the reaction was stretched out by using 2-chloro-3-formylquinolines, **1a,b**, acetophenones, **2a-d,f** in the presence of 2 mL water under microwave irradiation. To accomplish the regioselective product, optimized conditions, variation of solvent, nano TiO₂ catalyst, the catalyst loading for, **4a** from **1a** (2 mmol) and **2a** (5 mmol) was investigated (see scheme 3). In like manner, amongst the tested solvents (Table 3) water was discovered to be better, economically viable and offered a high yield of the desired product, **4a**.

In the like way, the nano TiO₂ catalyst with a loading of 5mg was the best optimized condition (Table 3, entries 11-13) amongst the tested catalyst loads. The NaOH initiates the reaction and nano TiO₂ assumes a synergistic role in water under microwave irradiation, accelerating the reaction rate and increasing the product yield. The isolated yields are tabulated (Table 4). All the synthesized compounds were well characterized by various spectroscopic methods such as FTIR, ¹H NMR, ¹³C NMR, DEPT -135, 2D H-H, C-H COSY and HRMS spectra. In the FTIR spectrum, the corresponding functional group characteristic peaks were observed at 3462 (N-H), 1658 (HN-C=O) and 1678 (C=O) cm⁻¹ attributable to the stretching frequencies of **4a**. Additionally, the product **4a**, was affirmed by the presence of NH proton (HN-C=O) peak and carbon peak (HN-C=O) respectively at δ 10.79 in proton and 163 in carbon NMR spectra. In the DEPT-135 spectrum the aliphatic C-H carbons of methine C-3 (CH) indicated an up peak at δ 34.52 ppm, the symmetric methylene C-2 and C-4 (CH₂) down peaks at 41.41 ppm as seen in fig 2b (see supporting documents). However, in the compound, **3a** the corresponding (CH) up peak and (CH₂) down peaks were observed at δ 33.95 and 42.51 ppm respectively. The HRMS spectrum of the compound, **4a** demonstrated a peak at *m/z* 395.1512 [M⁺] attributable to the molecular formula of C₂₆H₂₁NO₃ calculated *m/z* 395.1521 [M⁺] confirming the proposed structure.

The ¹H NMR of **3a** showed a multiplet centered at 4.50 ppm attributable to H-3 in both the chloro and oxo analogues of diketones. The compound, **3a** likewise showed two magnetically nonequivalent diastereotopic protons of a methylene group (H_a/H_b at C-2 and C-4), at 3.58-3.664 ppm, coupled with one another and thusly with vicinal methine proton H-3 and created two double doublets merged together (Fig 2a-e). Nonetheless, in the oxo analogues, **4a** two doublet of doublets differentiated clearly owing to the presence of an anisotropic effect (adjacent NH-C=O to the H-3 proton) and attributable to the electron withdrawing keto groups (adjacent to the methylene carbon protons of C-2 and C-4). The electron density environment available gets coupled with H_a/H_b and one another as additionally with H-3 (**4a**) (Fig 2a-e). The aromatic protons appeared in the range 6.8–8.17 ppm. The ¹³C NMR showed weak signal at 197 and 198 ppm, attributable to symmetric carbonyl carbons at C-1 and C-5 (**3a** and **4a**). The chemical shifts of aromatic carbons appeared in the range 115.0–149 ppm. Then, again, for the fluoro and methoxy substituent containing chloro and oxo derivatives, aromatic carbons were seen in the range 163.45–167.07 ppm owing to the more electronegativity of oxygen and fluorine. The signal observed at 41.2–42.9 ppm was attributable to symmetric methylene carbons of C-2 and C-4. The signal appeared at 29–34 ppm indicating C-3. In the oxoanalogue owing to an additional NH-C=O group that showed a signal at 163–167 ppm and furthermore displayed coupling with the neighboring protons at C-2, C-3, C-4 as seen in the overlap spectra of the chloro and oxoanalogue as well (see supporting documents). In this present study, we have attained one-pot three component tandem Aldol condensation/ Michael addition reactions and Hydrolysis/ Aldol condensation/ Michael addition reactions involving acetophenones and 2-chloro-3-formylquinolines that afford the regioselective 1,5-dicarbonyl products.



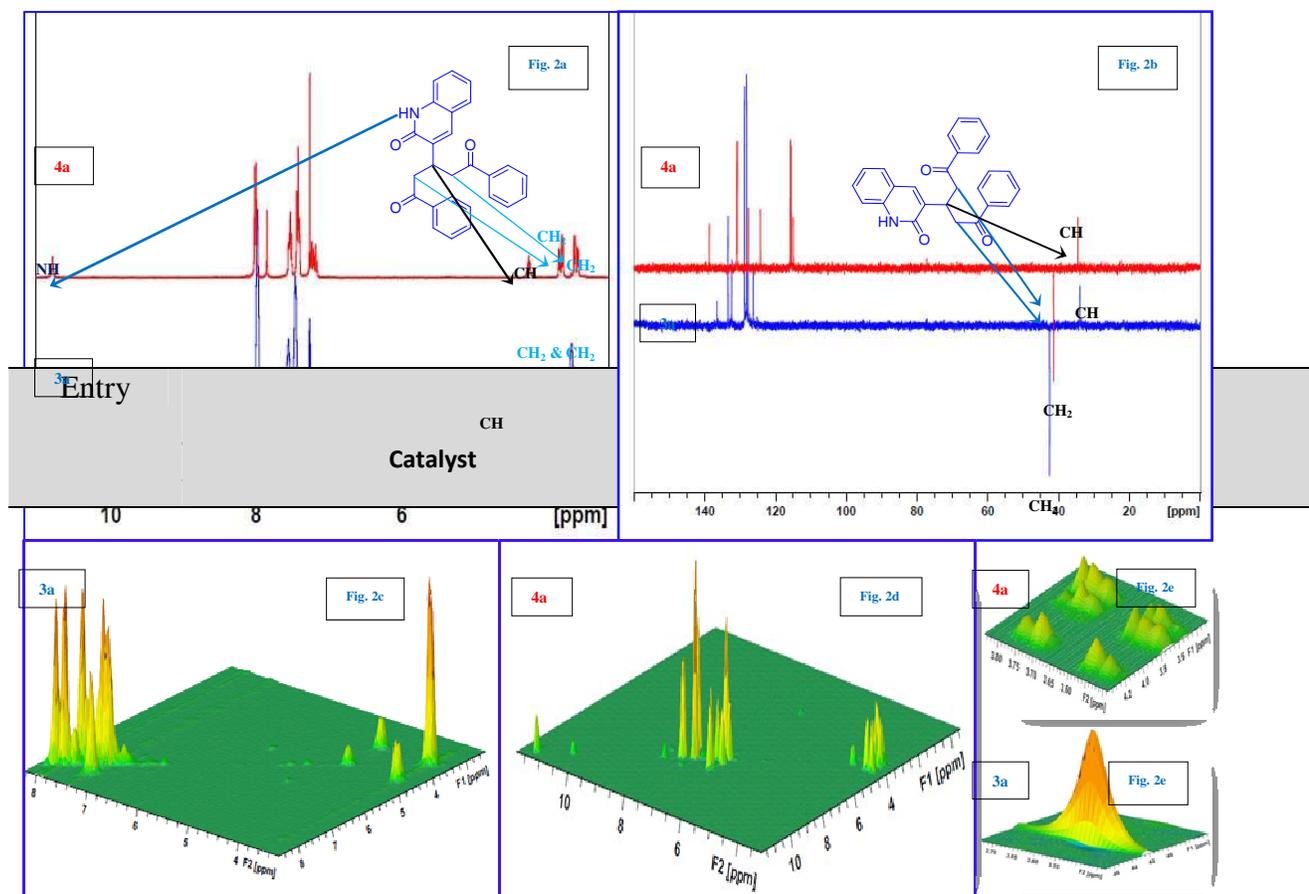


Fig 2 a) The overlap spectrum of proton NMR(**3a** and **4a**); b) The overlap spectrum of DEPT-135(**3a** & **4a**); c) 2D COSY spectrum of **3a**; d) 2D COSY spectrum of **4a** and e) 2D COSY expansion spectrum of merged two doublet of doublets (**3a**) and separated two doublet of doublets (**4a**).

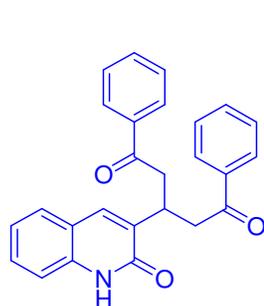
	Metal oxide	Quantity mg		MW ^b	Conv ^c
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2	TiO ₂	1	0	NR	NR
3	TiO ₂ or ZnO	0	1	5	NR
4	TiO ₂	1	1	15	NR
5	ZnO	1	0	NR	NR
6	ZnO	1	1	10	NR
7	TiO ₂	1	2	21	
			3	23	NR
			5	29	
8		2	1	26	Trace
	TiO ₂	3		32	
		5		38	
9		2	1	15	NR
	ZnO	3		20	
		5		35	
10	TiO ₂ nano	1	1	35	NR
11		2	1	46	Trace
	TiO ₂ nano	3		50	
		5		84	
12		2		20	Trace
	ZnO nano	3	1	24	
		5		40	
13	TiO ₂ nano	5	1	35, 43, 84 ^e	NR

Table 3 Water mediated reaction -Selection of catalyst, catalyst loading and heating method^a

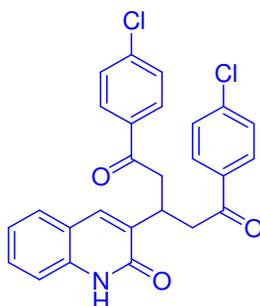
^a2-Chloroquinoline-3-carboxaldehyde, **1a** (2 mmol), acetophenone, **2a** (5 mmol), water 2mL, ^bMicrowave irradiation at 800 W, 30 min.

^cethanol-water 4mL (1:1), reflux, 3h, ^dNR-No reaction, ^eyields respectively for microwave irradiation at 300, 500, 800 W.

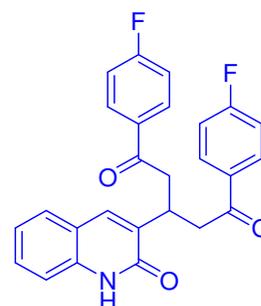
Table 4 Microwave assisted, water mediated synthesis of oxo analogue of 1,5-diones^a



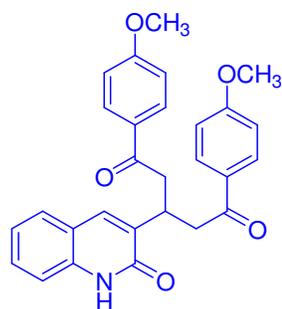
4a, 30 min, 84 %



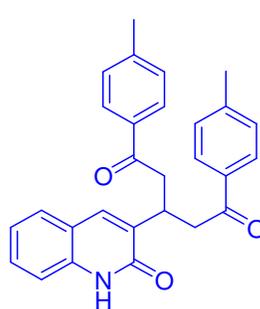
4b, 27 min, 80 %



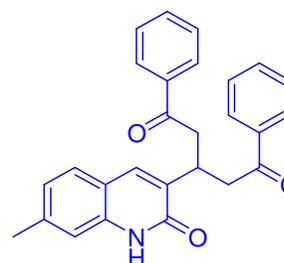
4c, 30 min, 79 %



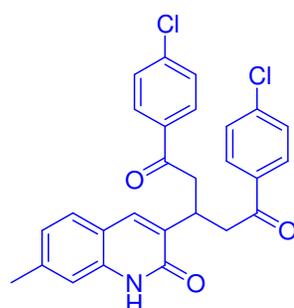
4d, 25 min, 81 %



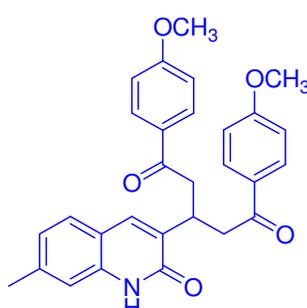
4e, 28 min, 78 %



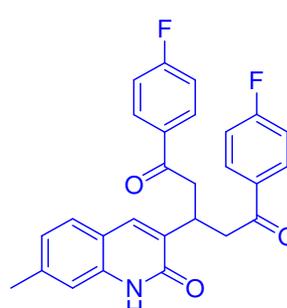
4f, 29 min, 83 %



4g, 30 min, 77 %



4h, 28 min, 85 %



4i, 30 min, 74 %

.^a2-Chloroquinoline-3-carboxaldehydes, **1a,b** (2 mmol), acetophenones, **2a-d,f** (5 mmol), 1mg of NaOH, 5mg of TiO₂, 2mL water, MW irradiation at 800W

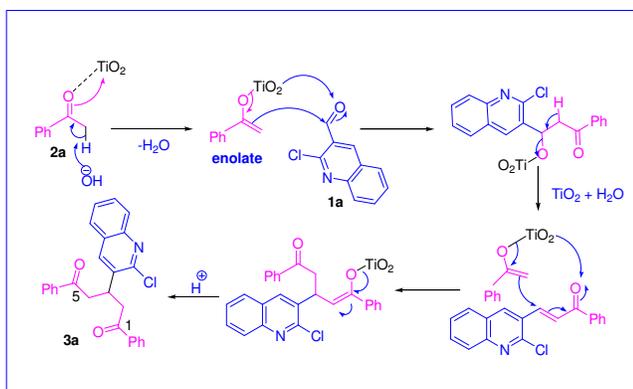
Mechanism

A conceivable mechanism for the regio-selective domino synthesis of 3-(1,5-dioxo-1,5-diphenylpentan-3-yl)quinoline, **3a** and 3-(1,5-dioxo-1,5-diphenylpentan-3-yl)quinolin-2(1H)-one, **4a** is represented in scheme 4 and 5.

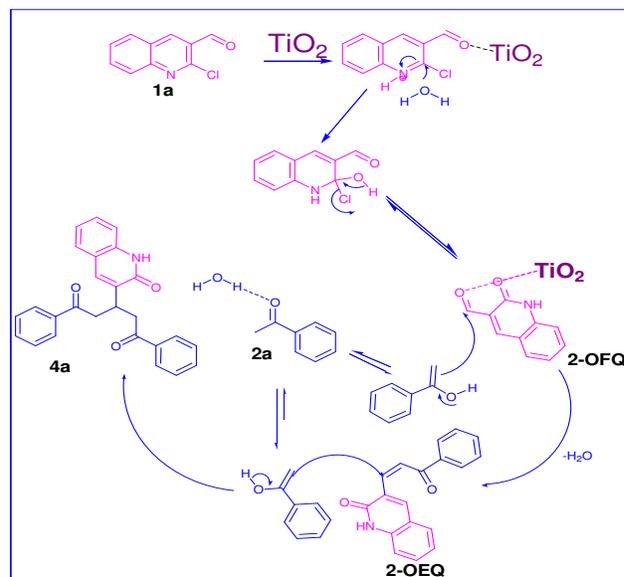
In the first step of the water free or no solvent condition, the reaction was initiated by NaOH and enhanced by the TiO₂ nanoparticles, bringing out the formation of Michael acceptors, enone (through the enolate) from the corresponding acetophenone, **2a** and 2-chloro-3-formylquinolines, **1a**. Under the influence of microwave irradiation and the TiO₂ nanoparticles, the enones, then experienced 1,4-Michael addition reaction with the Michael donors, acetophenones to offer the desired diketones, **3a**.

It is proposed that Ti(IV) on coordination with the carbonyl group (acetophenone) have brought out a dark reddish brown colored transition metal complex that produced an enolate ion, by abstracting the proton by base (see scheme 4). These transition metal complexes, on coordination with the aldehyde, increased the electrophilicity of the carbonyl carbon of aldehyde and making it susceptible for the intermolecular nucleophilic attack by an enolate ion. Further, the dehydration process has resulted in the desired product, **3a**. It must be noted that the byproduct water formed in the enone formation is not enough to start the hydrolysis of the chloro functionality of the starting material 2-chloro-3-formylquinolines.

Regardless, in the presence of excess water, in one-pot tandem reaction, the water molecules at first, get adsorbed on the surface of the TiO₂ and are stabilized by intermolecular hydrogen bonding. The adsorption/desorption of water molecules occurs reversibly on cooling/heating. Henceforth, in the first step under the microwave heating, the water molecule desorbed from the TiO₂ nanoparticles surface involves in the hydrolysis of 2-chloroquinoline, **1a** to hydroxylquinoline that tautomerize to the 2-oxoformylquinoline, **2-OFQ** (see scheme 5). Further, the formation of Michael acceptor, enone **2-OEQ** was enhanced by the TiO₂ nanoparticles, which, on subsequent addition reaction with the Michael donor, acetophenone, **2a** offered regio-selectively the desired oxodiketones, **4a**. It must be noted that the byproduct water formed in the enone generation is insufficient to start the hydrolysis process.



Scheme 4: Plausible mechanism for the formation of 1,5-dione



Scheme 5: Plausible mechanism for the formation of 1,5-dione

Conclusions

To conclude, an effective one-pot three components, nano TiO₂ catalyzed synthesis of diverse 1,5-diones are reported. The advantages of the present methodology included different eco-friendly features such as no solvent or universal solvent water usage, catalytically active TiO₂ nanocrystallites. The catalyst is water insoluble, easily separated or recovered from the reaction mixture after completion of the reaction and by dissolving the products using suitable solvents. The protocol is scalable and has the main advantages of simplicity of work-up, mild reaction conditions, reusable catalyst and noteworthy yields.

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Experimental

General procedure for the synthesis of 3-(1,5-dioxo-1,5-diphenylpentan-3-yl)quinolin-2(1H)-one

In a typical reaction, a mixture of TiO₂ nanocatalyst (1mg), NaOH (1mg), 2-chloro-3-formylquinolines (2mmol), acetophenones (5mmol), was taken in a minimum amount of dichloromethane and dried gently. Then the mixture was microwave irradiated at 500W for 13 min. After the completion of the reaction as monitored by TLC, the mixture was again dissolved in dichloromethane and filtered to separate the catalyst. The solvent was evaporated to obtain the crude product, **3a** and then re-crystallized from methanol.

For the oxo analogue, **4a** the same procedure was followed, however, in the presence of 2mL water and microwave irradiated at 800W for 30 min.

Notes and references

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