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Photocatalytic synthesis of 2-amino-4,6-diarylpyrimidines using nanoTiO_2

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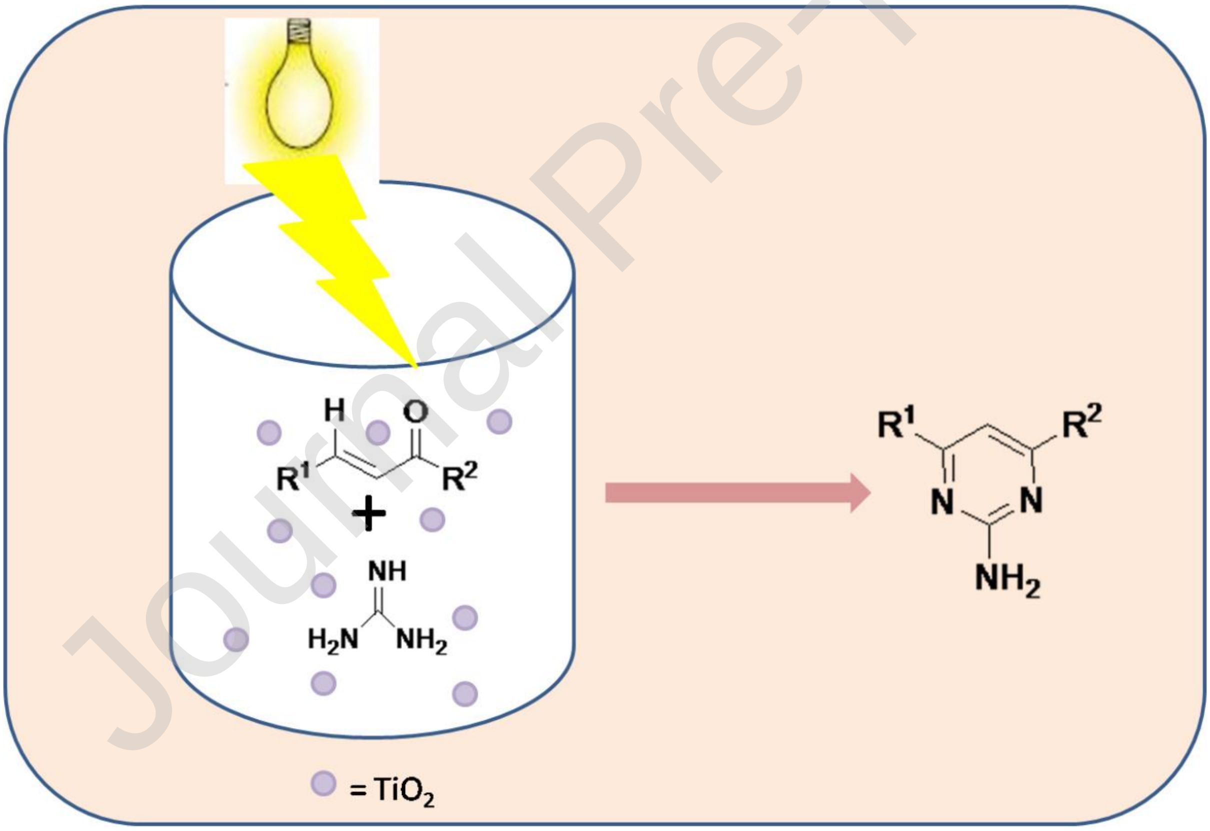
Graphical abstract

Synthesis of 2-amino-4,6-diarylpyrimidines were carried out by using reusable nanophotocatalyst TiO_2 at λ_{max} of 365 nm in ethanolic medium. The method offers excellent yield in 20 min at room temperature. The method follows a green route by avoiding the use of toxic reagents and drastic reaction conditions.



Highlights

- 2-Amino-4,6-diarylpyrimidines were synthesised photocatalytically using nano TiO_2.
- The reaction could be completed with excellent yields within 20min.
- Use of strong basic conditions, toxic organic solvents and tedious experimental conditions could be avoided.
- The method is environmentally friendly by minimising waste production.
- The method follows a green route with low E-factor and high Eco-scale score.

Abstract

Photocatalytic synthesis of 2-amino-4,6-diarylpyrimidines was carried out by using nano TiO_2. The method follows a green route by avoiding the use of toxic organic solvents and tedious experimental conditions. Compared with conventional methods the present strategy offers excellent yield under UV irradiation for a period of 20 min in ethanolic medium. Only a small quantity of nanocatalyst (1 mol%) is sufficient to achieve the completion of the reaction. The nanocatalyst can be reused up to four reaction cycles without much loss in the activity.

Keywords: photocatalytic synthesis, photocatalyst, nano TiO_2, pyrimidine derivatives, green synthesis.

1. Introduction

Pyrimidine and its derivatives have engrossed the scientists due to their remarkable biological and therapeutic applications [1]. Many biologically and pharmacologically active molecules contain pyrimidine core. The fundamental building blocks of nucleic acids are pyrimidine bases like thymine, cytosine, and uracil and fused pyrimidine system (purine) in adenine and guanine [2]. Pyrimidine ring is present in many drugs such as imatinib, idoxuridine, trifluridine, zalcitabine and zidovudine, etc. [3, 4]. Many pyrimidine derivatives exhibit antibacterial, antifungal, anti-inflammatory, anticancer, antiviral, anti-allergic, antipyretic, analgesic, antioxidant activities [3, 5-10]. Due to their broad spectrum of applications in medical as well as biological fields, synthesis of pyrimidine derivatives received great attention.

Synthesis of pyrimidine derivatives by traditional thermal methods and advanced microwave assisted methods is well established [11-16]. But most of these methods make use harmful organic solvents and tedious reaction conditions. Moreover, organic reactions without the use of risky experimental conditions have gained much attention for the past few years [17-21]. Currently the development of such approaches becomes the core part of scientific research and the use of green protocols in the chemical reactions is very important[22-25]. One such method includes the application of nanoparticles in synthesis as catalyst [26]. Use of inorganic metal oxides in organic synthesis is rapidly growing due to their ability in the enhancement of reaction rates, simplicity of operation and their availability at low cost and reusability [27-29]. Metal oxides such as SiO_2, Al_2O_3, ZnO etc. are normally used in organic synthesis [30-32]. The catalytic activity of these kinds of metal oxides in nanoform in organic synthesis was explored by many researchers in recent times [33-36]. There are several reports on the photocatalysed C-N coupling reactions. Ohtani et al. reported the photocatalytic coupling of amine with aldehydes to imines in presence of nanoTiO_2. Palmisano and co-workers reported the photocatalytic cyclization of lysine in presence of nanoTiO_2 to pipecolinic acid. The intramolecular cyclization of the diaminodicarboxylic acid and the hydrazone via C-N coupling in the presence of the photocatalyst nanoTiO_2 has also been reported by Kisch et al. [37-39]. But the investigations of photocatalytic activity of TiO_2 nanoparticles in the synthesis of pyrimidine derivatives are rarely reported. The present work is an attempt to exploit the photocatalytic activity of TiO_2 nanoparticles in the synthesis of 2-amino-4,6-diarylpyrimidines.

We have carried out the synthesis of a series of substituted pyrimidines by both traditional thermal method as well as microwave assisted method. Then the photocatalytic effect of TiO_2 nanoparticles on the synthesis of pyrimidine derivatives was also explored. This method offers high yield, short reaction time, reduced cost, easy work-up and mild reaction procedure under environmentally friendly conditions avoiding toxic waste production.

2. Experimental

2.1 Chemicals and instruments

All the substrates and reagents used including guanidine hydrochloride, aldehydes and ketones were purchased from Spectrochem Chemicals Pvt. Ltd. India. All solvents used were purchased from local suppliers and were purified before use by following the standard procedures. The Fourier Transform infrared spectra (FT-IR) were recorded on a Perkin-Elmer 400 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra of the samples were taken using Bruker Avance DPX-300MHz FT-NMR spectrometer. Scanning electron microscopic (SEM) analyses were performed on a JEOL-JSM-6390A SEM analyzer. The high resolution mass spectra (HRMS) were recorded HRMS using XEVO G2 Q-TOF (Waters) mass spectrometer. XRD analysis was conducted on a PANalytic X'PERT-PRO X-ray spectrometer. Melting points were recorded on MPHT melting point apparatus and are uncorrected.

2.2 Synthetic procedures

2.2.1. Synthesis of TiO_2 nanopaticles

Titanium tetrabutoxide (1mL, 1.00 g/mL) was dissolved in ethanol (25 mL) and the solution was added to distilled water (250 mL) at 40°C with constant stirring. The pH of the solution was maintained at 1.5 with the addition of HCl. The obtained transparent colloidal solution was stirred overnight [40]. The solvent was then rota evaporated. The obtained TiO_2 nanopowder was collected, heated at 600 ^{o}C for 4 h, characterised by SEM, DLS & XRD and used for further studies.

2.2.2. Synthesis of 2-amino 4,6-diarylpyrimidines catalysed by nanoTiO_2

Initially chalcones were synthesised by reported procedure [41]. Guanidine (1 mmol) was treated with the chalcone component (1mmol) in presence of TiO_2 nanoparticles (1 mol%, 3.33 mg) in ethanol under UV irradiation at λ_{max} 365 nm for 20 min. The catalyst was then filtered off and the solution was poured into ice cold water (30 ml). The crude solid product was collected by filtration and recrystallized from ethanol to afford the pure product.

3. Results and discussion

3.1 Synthesis and characterisation of TiO_2 nanoparticles

TiO_2 nanoparticles were synthesised according to the reported procedure and was characterised and used as photocatalyst for the synthesis of the pyrimidine derivatives. The synthesis was carried out by the hydrolysis and condensation of the precursor, titanium tetrabutoxide [42]. At first titanium tetrabutoxide was dissolved in ethanol and the resulted ethanolic solution was subsequently added to distilled water. In the aqueous medium hydrolysis of the precursor took place and subsequent polymerisation resulted in the formation of a three dimensional metal oxide network $Ti(OH)_4$, which was then condensed on calcination via the formation of oxo bridges between the Ti atoms and further olation leading to the formation of TiO_2 nanoparticles. The reported reaction mechanism is as shown below[42, 43].

$$Ti(O(CH_2)_3CH_3)_4+4H_2O \longrightarrow 2Ti(OH)_4+4CH_3(CH_2)_3OH \text{ (hydrolysis)}$$

$$Ti(OH)_4 \longrightarrow TiO_2.xH_2O+ (2\text{-}x)H_2O \text{ (condensation)}$$

The morphology of TiO_2 nanoparticles was analysed by scanning electron microscopy (SEM) and the average particle size was determined from dynamic light scattering (DLS) studies (**Figure 1**).

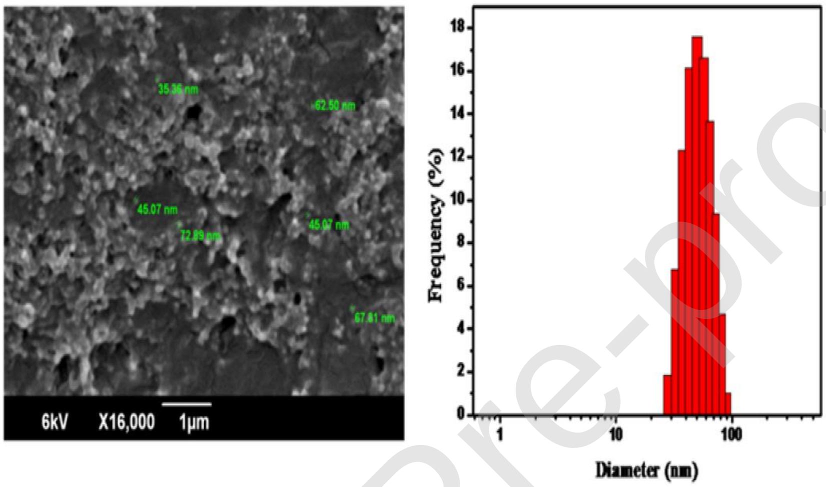


Figure 1. SEM and DLS graphs of TiO_2 nanocatalyst

From the DLS analysis the average particle size of the TiO_2 nanoparticles was found to be 49.9 nm confirming the formation of nanoparticles. The band gap of TiO_2 nanoparticle was determined by UV spectrophotometric studies and was found to be 2.8 eV from the Tauc's plot. The X-ray diffraction pattern of the synthesized TiO_2 nanoparticles is shown in Figure 1. The peaks of 2θ values at 25.23, 38.38, 48.46, 54.41, 62.62 and 68.57 indicate (101), (004), (200), (105), (211), (204) and (116) planes of anatase TiO_2. In the spectrum there is only one small peak at 2θ values of 27.48 (110 plane) indicate the presence of traces of rutile phase [44, 45].

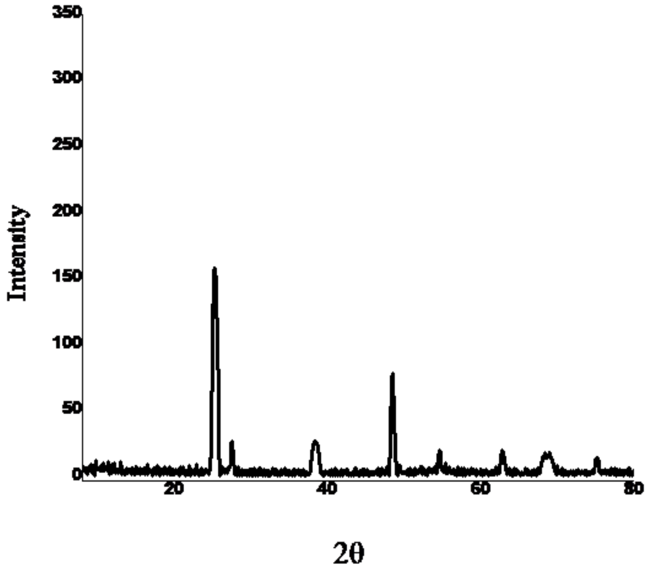
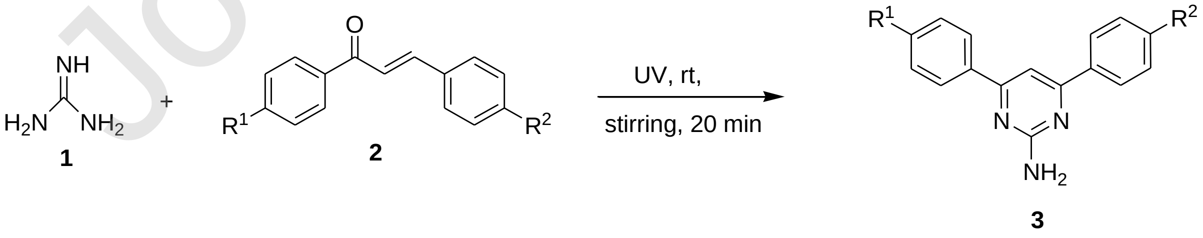


Figure 2. X-ray diffraction pattern of the synthesized TiO_2 nanoparticles

3.2. Synthesis of 2-amino-4,6-diarylpyrimidine 3c catalysed by nanophotocatalyst TiO_2

Chalcones **2** were prepared from substituted benzaldehydes and substituted acetophenones according to the reported procedure [41]. The synthesised chalcone, guanidine and 1 mol% of nanoTiO_2 were stirred in ethanol under UV irradiation having λ_{max} of 365 nm at room temperature for 20 min to afford 2-amino-4,6-diarylpyrimidine (**3**) (**Scheme 1**). After completion of the reaction, the nanocatalyst was removed by simple centrifugation and the supernatant liquid containing the product was poured into crushed ice and the product, 2-amino-4,6-diarylpyrimidine was precipitated out. The precipitated 2-amino-4,6-diarylpyrimidine was separated in moderate to excellent yield and further purified by recrystallisation from ethanol. By varying the substituents in chalcone moiety, a series of pyrimidine derivatives were synthesised.



Scheme 1.Synthesis of 2-amino-4,6-diarylpyrimidines catalysed by nanophotocatalyst TiO_2

In a typical reaction the 2-amino-4,6-diarylpyrimidine (**3c**) was synthesised from 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one and guanidine in the presence of the photocatalyst with a yield of 99%. The product was characterised using IR, NMR, HRMS and single crystal X-ray diffraction techniques.

Characterisation of 4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine (3c): FT-IR: The FT-IR spectral analysis shows broad absorption bands at 3320 and 3280 cm^{-1} corresponding to N-H stretching. The HRMS showed a base peak at 278.1293 indicating the formation of product (**Figure 3**).

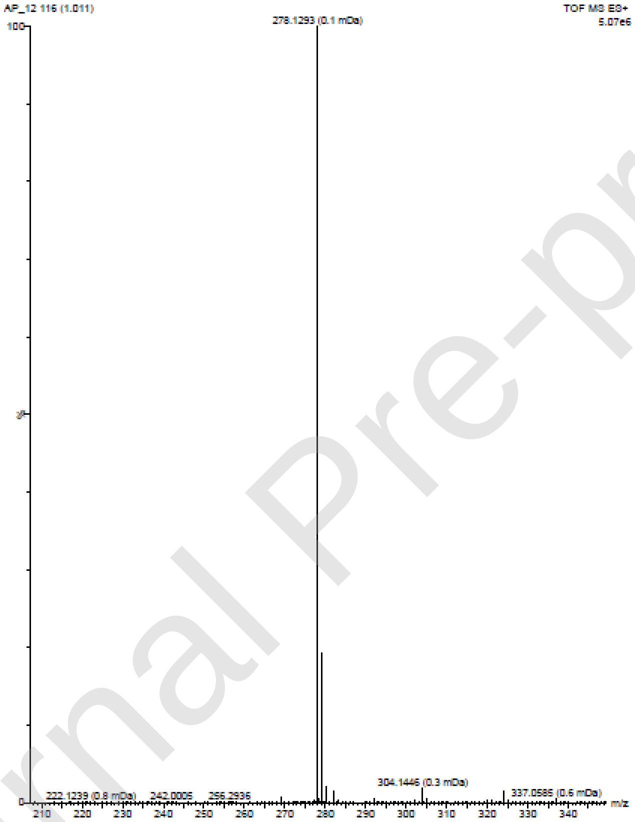


Figure 3. HRMS of 4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine **(3c)**

NMR: In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum a singlet appeared at δ 5.17 ppm corresponding to the two NH_2 protons. The OCH_3 protons resonated at δ 3.88 ppm as a singlet. The C5 proton in the pyrimidine ring appeared as a singlet at δ 7.02 ppm. Peak at 6.99 ppm correspond to the protons ortho to the OCH_3 group. The signals corresponding to the remaining six aromatic protons appeared in the range δ 7.26 – 8.05 ppm confirming the formation of the product (**Figure 4**).

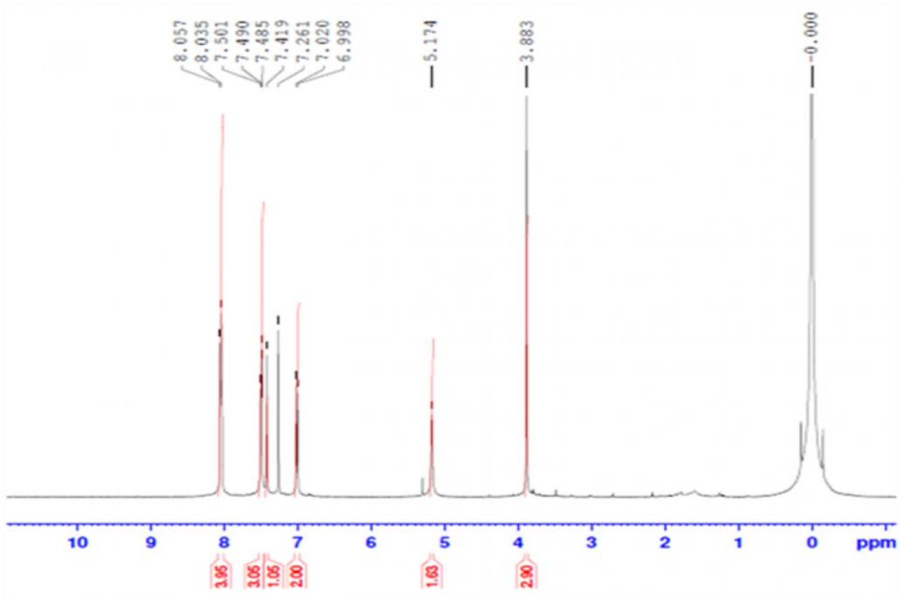


Figure 4.^{1}H NMR spectrum of 4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine **(3c)**

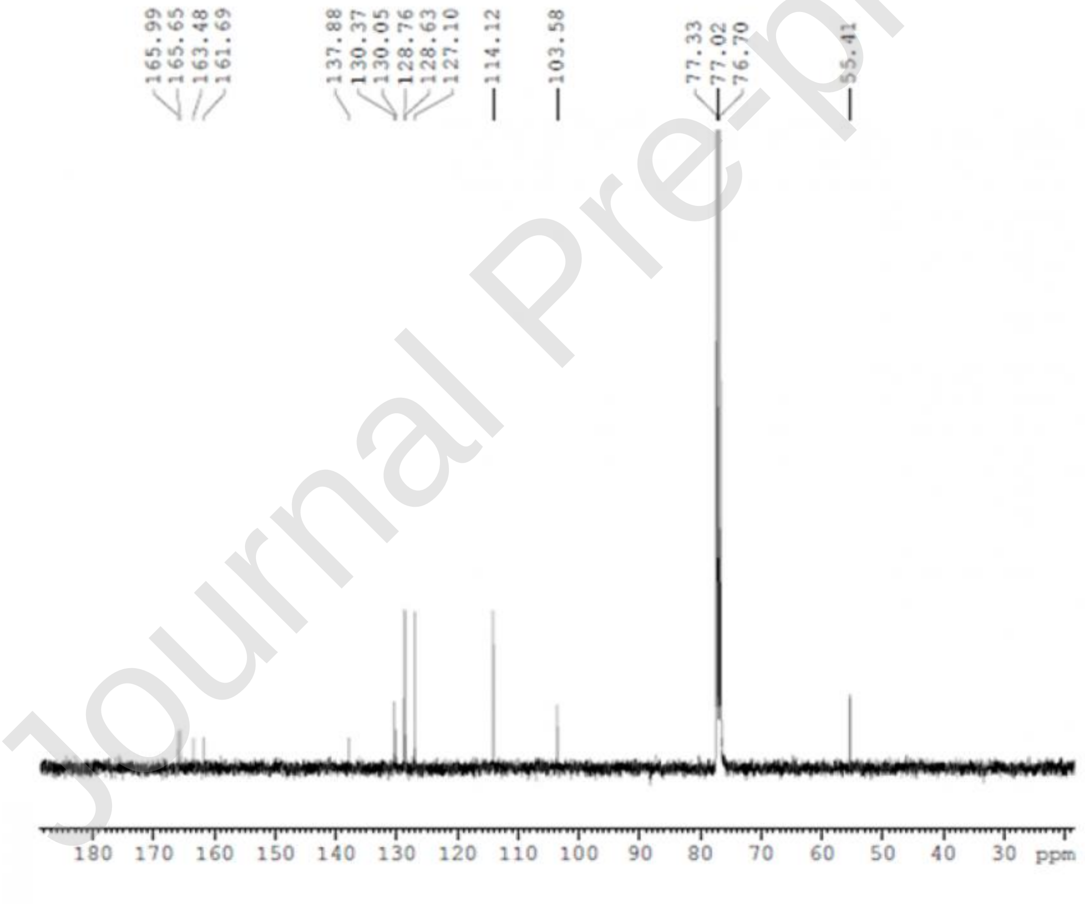


Figure 5.^{13}C NMR spectrum of 4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine **(3c)**

The ^{13}CNMR (100 MHz, $CDCl_3$) spectrum also supports the structure of the product from the following peaks at δ 165.99 ppm (C2), 161.69 ppm (C4), 103.58 ppm (C5), 165.65

ppm (C6) of the pyrimidine ring and 55.41 ppm (OCH_3). The OCH_3 substituted carbon appeared at δ 163.48 ppm. The *ortho*- carbon of the OCH_3 group resonated at δ 114.12 ppm. The remaining nine aromatic carbons resonated in the range δ 127.10 – 137.88 ppm (**Figure 5**). The single crystal XRD data also confirms the structure of product (**Figure 6**).

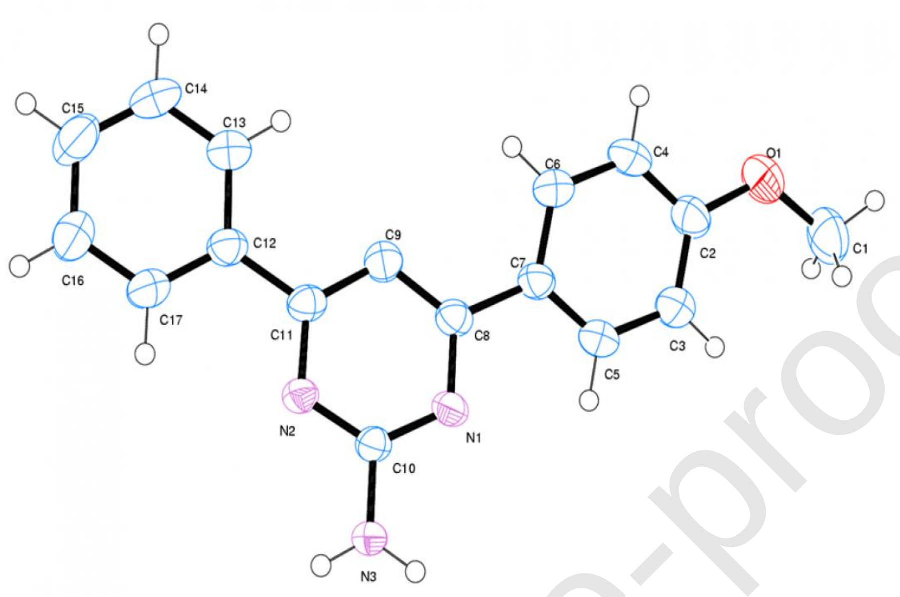


Figure 6. ORTEP diagram of single crystal X-ray diffraction structure of 4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine **(3c)**

3.3 Optimisation Studies

The synthesis of pyrimidine derivatives from 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one and guanidine in ethanolic medium in presence of TiO_2 nanophotocatalyst was selected as the model reaction to study the catalytic activity of the nanoTiO_2.The reaction conditions were optimised on the basis of reaction time and the amount of nanocatalyst used. Initially a mixture of equimolar quantities (1mmol) of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one and guanidine hydrochloride were reacted in presence of 1 mol% of TiO_2 nanophotocatalyst at λ_{max} of 365 nm. The progress of the reaction was monitored by thin layer chromatography (TLC). After 20 min the reaction mixture was taken, the product was isolated and the yield was found to be 99%.

3.3.1 Optimisation of catalyst concentration and time

Varying the amount of nanocatalyst from 0.2 mol% to 2.0 mol%, a series of experiments was carried out using 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one and guanidine in ethanolic medium. The results are summarised in the **Table 1**. The yield of the product formed increased with increasing the amount catalyst loading. The yield was 99% when the amount of catalyst reached 1 mol% for a reaction time of 20 min. There was no increase in the yield of the product with further increase in catalyst loading. The maximum dispersion of nanocatalyst will be attained only at a particular concentration [46]. Further increase in concentration may cause the agglomeration of nanoparticle.

The optimum reaction time for the synthesis was also investigated. The synthesis was carried out by varying the reaction time from 10 to 30 min. The maximum yield of the product was observed at 20 min with a catalyst concentration of 1 mol% (**Table 1**). Further increase in time has no effect on product yield. A blank reaction was also carried out in the absence of nanocatalyst TiO_2 under the same conditions and no product formation was observed in such case indicating the role of the nanocatalyst in the reaction. The reaction was also conducted in the absence of UV light but in the presence of the catalyst nano TiO_2. In this case also no product was formation proving that the cyclisation is taking place in the presence of UV irradiation.

By this photocatalytic method twenty one 2-amino-4,6-diarylpyrimidines (**3a-3u**) were synthesised. All the products were obtained in moderate to excellent yields under mild green reaction conditions (**Table 2)**. All the products were characterised by IR, NMR and HRMS analysis.

3.5. Regeneration and reusability

The regeneration and reusability of the catalyst after each step was checked by separating the catalyst after completing the each reaction cycle by centrifugation. The collected catalyst was then purified by washing with ethanol and kept at hot air oven for 1h at 100^{o}C. The reusability of the spent nanocatalyst was investigated by carrying out the synthesis of 2-amino-4,6-diarylpyrimidines under the same catalytic conditions described above after regenerating the catalyst and compared with the fresh catalyst. The catalyst was then analysed by SEM and DLS analysis, which confirms the nano size of catalyst up to the fourth reaction cycle.

The catalyst regenerated could be used for four cycles of synthesis without much loss in the catalytic activity and after the fourth cycle, reduction in catalytic activity reduced and the yield of the product was decreased by 15 % (**Table 3)**. After the fourth reaction cycle massive agglomeration of nanoparticles had taken place which was proved by SEM and DLS studies.

After the fourth cycle, DLS and SEM analyses of the recycled catalyst were carried out and were compared with the freshly prepared catalyst (**Figures 7 & 8**). Formation of aggregates of catalyst with recycling was supported by the SEM images. Similarly DLS studies reveal that the catalyst tends to form agglomerates with recycling. This was confirmed from the increase of average particle size of catalyst to 273.6 nm after the fourth cycle. These results confirmed the large agglomeration of nanoparticles which was the reason for decreased catalytic activity.

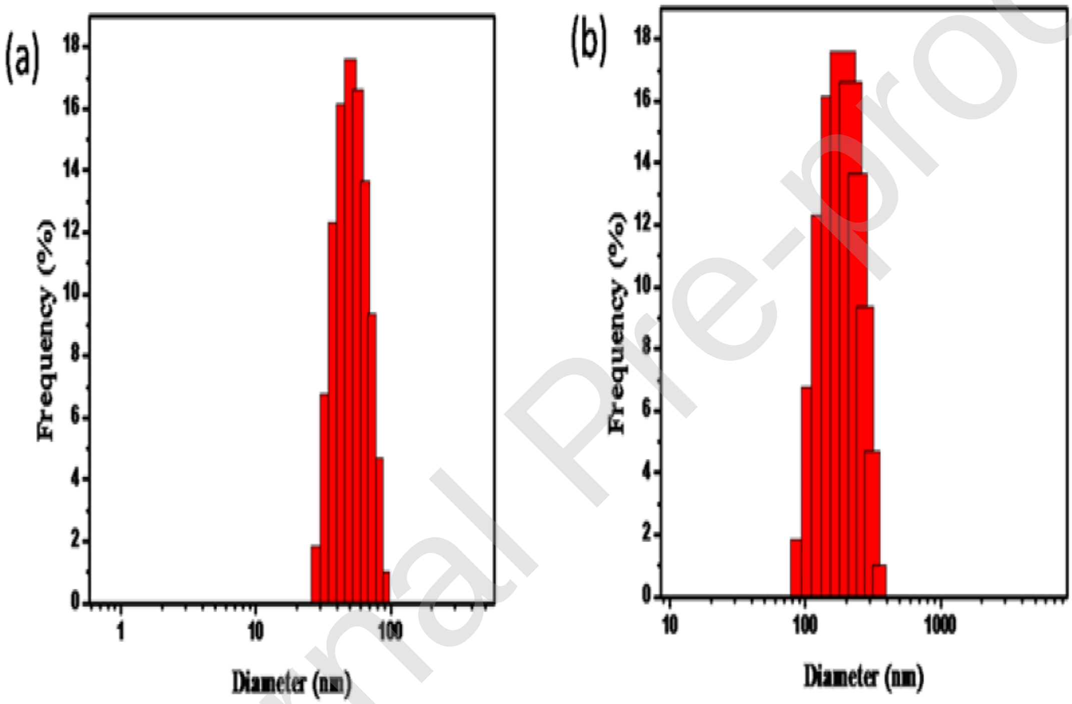


Figure 7. DLS studies nanocatalysts indicating the size (nm) of TiO_2 NPs (a) before reaction average particle size = 49.9 nm (b) after fourth cycle average particle size = 273.6 nm

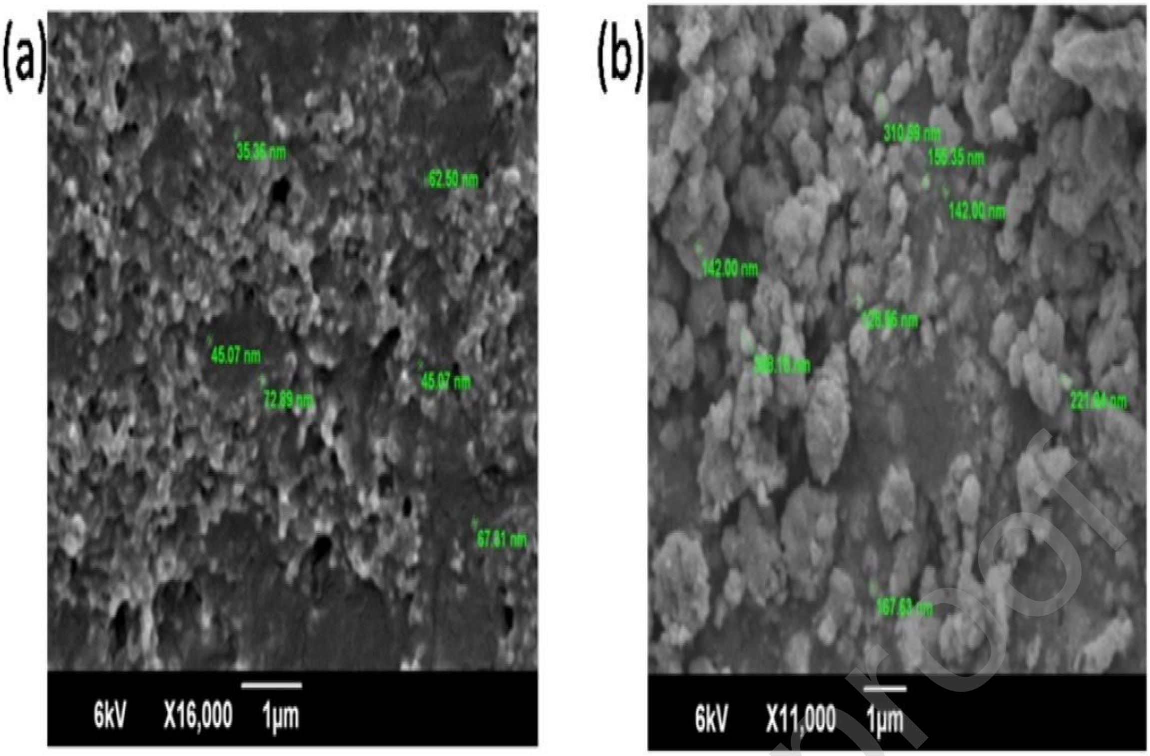


Figure 8. SEM images of TiO_2 nanocatalyst showing the morphology of NPs (a) before reaction (b) after fourth cycle

The advantages of the present method includes high yield, ease of purification, shorter reaction periods, mild reaction conditions, etc. indicating that the method follows a green synthetic protocol.

A plausible mechanism for the photocatalysed reaction is shown in **Figure 9**. The UV light energy promotes the electronic transition in TiO_2 from valence band to the conduction band. The interaction of this electron with guanidine hydrochloride **I** provides a radical anion **II.** This radical anion **II** is then added to chalcone molecule forming the radical anion **III** which undergoes intramolecular cyclisation affording the 2-amino-4,6-diarylpyrimidine product.

To confirm the formation of radical intermediates, the reaction was performed in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO). No product formation was observed in presence of the radical scavenger proving the formation of radical intermediates.

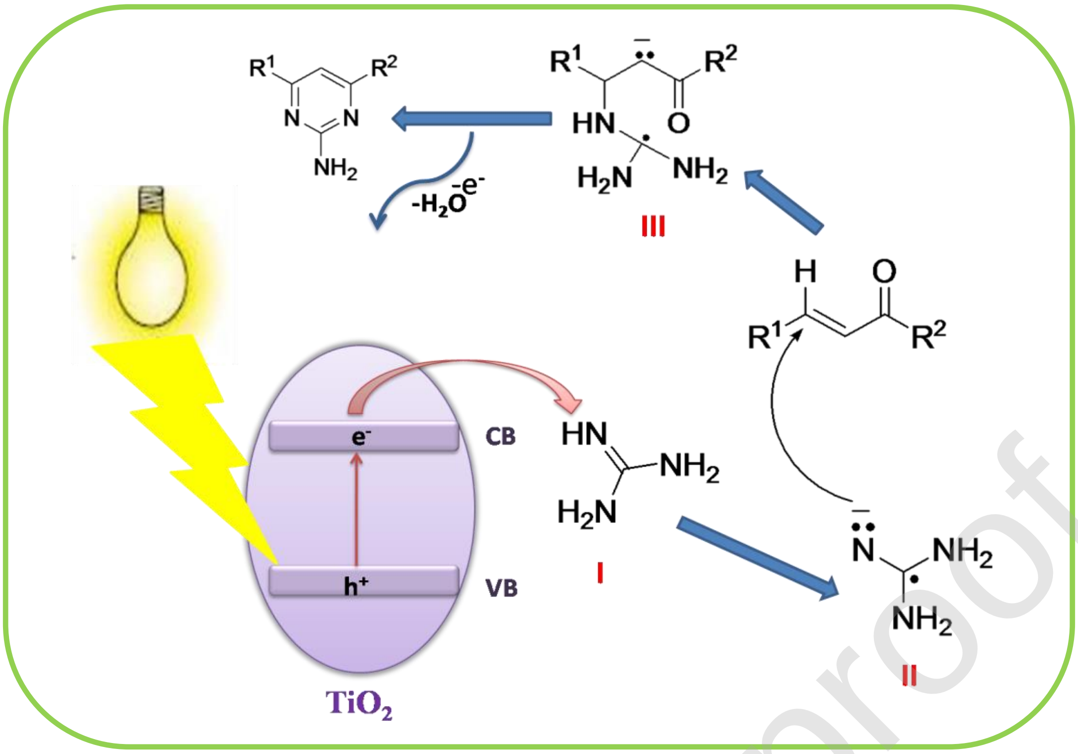


Figure 9. Plausible mechanism for the synthesis of 2-amino-4,6-diarylpyrimidine by nanophotocatalyst TiO_2

The E-factor and Eco-scale score calculations of the present study were carried out, these are the parameters which determine the greenness of an organic synthesis [47]. In order to calculate these parameters, synthesis of pyrimidine derivatives from 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one and guanidine hydrochloride was selected as model reaction. The E-factor of the present study was observed as 0.012 and Eco-scale score was 83.5 [47-48]. The lower E-factor value (i.e, ~ 0) indicates less the waste generation and more green the procedure. Similarly high Eco-scale score (i.e, ~ 100) indicates the ideal behaviour of the reaction [48]. The advantages of the present method includes high yield, ease of purification, short reaction time, mild reaction conditions, low E-factor, high Eco-scale score etc. These factors indicate that the present method follows a green synthetic protocol.

3.4. Advantages of the present method: a comparison with conventional and microwave assisted method

The present photocatalytic synthesis method was compared with conventional and microwave assisted synthesis on the basis of reaction conditions, time taken for the reaction and product yield. The conventional and microwave assisted method completed with the aid of strong basic medium, which could be avoided in nanocatalysed synthesis. Similarly conventional and microwave assisted synthesis used drastic reaction conditions such as high temperature. But in nanocatalysed synthesis only room temperature was sufficient for the completion of the reaction. The time required for conventional synthesis was 3 h which could be reduced to 20 min in microwave assisted method. But with this time under mild reaction conditions an increased yield was observed in nanocatalysed synthesis. The E-factor and Eco-scale score for conventional synthesis were calculated to be 0.23 and 66. Similarly for microwave assisted syntheses the values were estimated to be 0.17 and 61. The results prove the more greenness of present photocatalysed synthesis over conventional and microwave assisted synthesis.

4. Conclusion

2-Amino-4,6-diarylpyrimidines could be synthesised in presence of the photocatalyst nanoTiO_2 in ethanolic medium. The nanocatalysed synthesis avoids the use of tedious reaction conditions and high yields of the product could be achieved. Other major advantages of the present method include short reaction time, low cost and easy work-up. The method is also environment friendly by avoiding the harmful reaction conditions, toxic waste production, etc. The catalyst could be recycled and reused.

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Table 1.Optimisation studies of nanophotocatalysed synthesis of **3c**

Entry	**Mol % of TiO_2nanocatalyst**	**Yield (%)**			
		10 min	**20 min**	**25 min**	**30 min**
1	0.2	23	40	42	42
2	0.4	38	48	50	50
3	0.8	67	75	78	78
4	1.0	81	99	99	99
5	1.2	81	99	99	99
6	1.5	81	99	99	99
7	2.0	81	98	99	99

Table 2. Yields of 2-amino-4,6-diarylpyrimidines (**3a-3u**) synthesis catalysed by photocatalyst TiO_2 for 20 min.

Compound	**R^1**	**R^2**	**Yield (%)**
			Photocatalysed synthesis (20min)
3a	H	H	62
3b	H	CH_3	74
3c	H	OCH_3	99
3d	H	NO_2	81
3e	H	Cl	72
3f	H	NMe_2	62
3g	H	CN	83
3h	Cl	H	71
3i	Cl	CH_3	79
3j	Cl	OCH_3	84
3k	Cl	NO_2	83
3l	Cl	Cl	76
3m	Cl	NMe_2	36
3n	Cl	CN	72
3o	NO_2	H	83
3p	NO_2	CH_3	75
3q	NO_2	OCH_3	85
3r	NO_2	NO_2	71
3s	NO_2	Cl	82
3t	NO_2	NMe_2	32
3u	NO_2	CN	79

Table 3. Catalytic recyclability check up to fourth cycle

No of cycles	Yield (%)
1	99
2	98
3	92
4	91
5	84