RASĀYAN *J. Chem.*
Vol. 19 | No. 3 | 1876-1882 | July-September | 2026
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

AN EFFICIENT SYNTHESIS OF BENZO[h]QUINOLINE-3-CARBONITRILES USING GREEN NANO-TiO_2UNDER SONICATION

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ABSTRACT

In this research article, we have reported the green procedure for the synthesis of TiO_2 nanoparticles using the leaf extract of *Raphanus sativus*as a natural reducing and stabilising agent. The structure and morphology of synthesised nanoparticles (NPs) have been confirmed by various techniques, including FT-IR, SEM, TEM, XRD, and EDX analyses. The synthesised TiO_2 NPs were utilised as an efficient green heterogeneous catalyst for the synthesis of benzo[h]quinoline-3-carbonitrile derivatives *via* a four-component reaction of benzaldehyde, malononitrile or α-cyanoacetic ester, α-tetralone, and ammonium acetate under sonication in an aqueous medium. The present optimised reaction conditions afforded a high yield of desired products within a short reaction time, along with reasonable purity. Additionally, the nanocatalyst was readily recoverable and could be reused for multiple cycles.

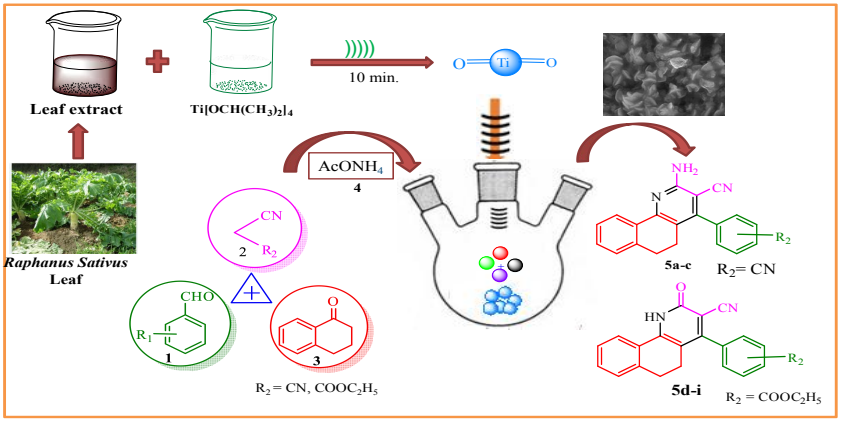
Keyword: Green Synthesis;Sonochemistry, TiO_2Nanoparticles, *Raphanus sativus* Leaf Extract; Benzo[h]quinoline-3-carbonitrile

RASĀYAN*J. Chem.*, Vol. 19, No.3, 2026

INTRODUCTION

Modern synthetic organic chemistry depends significantly on the use of heterogeneous catalysts, particularly nanocatalysts, because of their remarkable benefits, which include high catalytic efficiency, less toxicity, ease of separation, and further use of the catalyst.[1] Titanium dioxide (TiO_2) nanoparticles have been identified as an eco-friendly heterogeneous catalyst and reported to catalyse various organic reactions due to their unusual physicochemical properties.[2] Among nitrogen-containing heterocyclic compounds, quinoline and its derivatives have emerged as highly significant scaffolds in medicinal and pharmaceutical chemistry[3]. The 2-amino-5,6-dihydro-4-phenyl-benzo[h]quinoline-3-carbonitrile derivatives are potent compounds exhibiting significant anticancer activity and effective inhibition of matrix metalloproteinases.[4] The earlier reports for the synthesis of 2-aminobenzo[h]quinoline derivatives include the classic Michael addition, either between malononitrile and 2-arylidene-1-tetralone or between benzylidene-malononitriles and α−τetralone.[5-6] Some reported approaches involve multicomponent reaction of aldehydes, malononitrile, α-tetralone, and ammonium acetate using conventional and non-conventional methods using ultrasound irradiations.[7] Both methods have their respective advantages; however, they possess some drawbacks. For instance, conventional synthesis involves the use of carcinogenic solvents such as toluene and employs acetic acid as a catalyst, and the use of a large excess of ammonium acetate, which raises environmental and safety concerns. On the other hand, sonochemical synthesis is typically carried out using low-intensity ultrasonic (LIU) cleaning baths, which often suffer from limited power availability, leading to reproducibility issues.[8] As part of our ongoing efforts to develop sustainable synthetic methodologies for heterocycles,[9] we report herein an efficient synthesis of substituted benzo[h]quinoline-3-carbonitriles **5***via* a four-component reaction in the presence of a heterogeneous green TiO_2 catalyst in aqueous medium using a high-intensity probe sonicator (Scheme-1). As per our knowledge, this is the first report describing the synthesis of the target molecular system 5 using nanoparticles as a catalyst under sonication. To enhance the eco-friendliness of the overall process, the applied TiO_2 NPs were synthesised under sonication using Raphanus sativus (radish) leaf extract, having hydroxyl-rich phytochemicals.[10]

http://doi.org/10.31788/RJC.2026.1939720



Scheme-1: Synthesis of benzo[h]quinoline-3-carbonitriles using TiO_2 as a Catalyst

EXPERIMENTAL

General Information

The melting point of all synthesised compounds was taken on a digital melting point apparatus. The FT-IR spectra of nano-TiO_2 and synthesised compounds were recorded on an Elmer spectrophotometer. The entire characterisation analysis of synthesised nano-TiO_2 was carried out using the instrumental facility of MNIT Jaipur, such as XRD (Panalytical X Pert Pro), Scanning Electron Microscope (FEI Nova NanoSEM 450) and Transmission Electron Microscope (Tecnai G2 20 (FEI) S-Twin). The ^{1}H NMR and ^{13}C NMR spectra of all synthesised compounds were recorded on Jeol Resonance using TMS as an internal reference at 400 and 100MHz, respectively. For the mass spectra, the Xevo G2-S Q Tof and TQD (water, USA) mass spectrometers were used. The Qsonica700 probe sonicator was used for carry out the chemical synthesis.

Preparation of Extract

The 20 g dried powder of Raphanus sativus leaves with 100ml distilled water was refluxed at 80°C temperature for 2 hours. Then the extract was cooled at room temperature and filtered using 1° Whatman filter paper. The resultant filtrate was used for the synthesis of nano-TiO_2 particles.

Green Synthesis of TiO_2 NPs

A mixture of 50 ml 0.5 mol·L^{-1} solution of titanium(IV)isopropoxide and plant extract (50 ml) was sonicated using a probe-type ultrasonic processor (Qsonica700, 20 kHz, 700 W, 12 mm tip) with 30-second on/off pulses at 50% amplitude for 10 minutes. The obtained gel was centrifuged at 6000 rpm for 20 minutes to remove residual plant material. The collected precipitate was washed with distilled water and dried at 60 °C, and calcinated at 400°C for 2 hours in a muffle furnace.

General Procedure for Synthesis of benzo[h]quinoline-3-carbonitrile Derivatives (5a-i)

A mixture of aromatic aldehydes 1 (5 mmol), malononitrile/ethyl cyanoacetate 2a/b (5 mmol), α-tetralone **3** (5 mmol), ammonium acetate (10 mmol) and nano-TiO_2 (10 mol %) with water (20 mL) was sonicated using a 12 mm probe at 50% amplitude (50W power). The reaction progress was checked by TLC, and after completion, the resulting reaction mixture was filtered, and the solid part obtained was washed with water, dried to afford the crude products. To remove the TiO_2 nanoparticles, the crude solid was suspended in ethyl acetate and centrifuged at 10,000 rpm for 25 minutes. The separated TiO_2 nanoparticles were washed with ethanol and dried for further use. The remaining part of ethyl acetate was concentrated, and the resulting crude product was recrystallised to yield the pure compounds 5a-i.

2-Amino-4-phenyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile5a

Yield = 90%; M.P. > 300℃ IR (cm^{-1}) 3472, 3355 (NH_2) 2210 (C≡N); ^{1}H NMR ($CDCl_3$) δ 2.59-2.63 (m, 2H, CH_2) 2.75-2.77 (m, 2H, CH_2), 5.22 (s, 2H, NH_2), 7.19-7.50 (m, 8H, Ar-H), 8.25-8.27 (m, 1H, Ar-H)

ppm; ^{13}C NMR ($CDCl_3$) δ 23.25, 27.04, 89.27, 125.06, 126.05, 126.66, 127.40, 127.63, 127.97, 129.30, 138.14, 152.13, 154.02, 157.15 ppm; MS (ESI) m/z 298.30 (M^++H).

2-amino-4-(4-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile5b
Yield = 93 %; M.P.> 300℃, IR (cm^{-1}) 3478, 3359 (NH_2) 2215 (C≡N); ^{1}HNMR ($CDCl_3$) δ 2.61-2.63 (m, 2H, CH_2 2.79-2.81 (m, 2H, CH_2), 5.25 (s, 2H, NH_2), 7.13-7.53 (m, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.48, 26.07, 90.27, 124.09, 127.08, 127.69, 128.43, 128.86, 127.99, 129.33, 138.17, 152.16, 154.08, 157.18 ppm.

3-amino-4-(3-chlorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 5c
Yield = 90%; M.P.> 300℃; IR (cm^{-1}) 3477, 3354 (NH_2) 2210 (C≡N); ^{1}HNMR ($CDCl_3$), d 2.79-2.78(m, 2H, CH_2) 2.78-2.76 (m, 2H, CH_2), 5.23 (s, 2H, NH_2), 7.11- 7.51 m (m, 8H, Ar-H) 8.26-8.28 (m, 1H, Ar-H) ppm; ^{13}CNMR ($CDCl_3$) δ 23.46, 27.05, 125.07, 126.06, 126.67, 127.41, 127.64, 127.98, 129.31, 138.15, 152.14, 154.03, 157.16 ppm.

2-oxo-4-phenyl-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile5d
Yield = 90%; M.p. > 300℃; IR (cm^{-1}) 3132 (NH), 2222 (C≡N), 1638 (C=O); ^{1}HNMR ($CDCl_3$): 2.51-2.53 (m, 2H, CH_2), 2.75-2.79 (m, 2H, CH_2), 7.15–7.54 (m, Ar-CH, 9H), 13.17 (bs, 1H, NH) ppm; ^{13}CNMR ($CDCl_3$) δ 24.82, 29.7, 95.52, 114.23, 117.12, 125.41, 126.12, 126.33, 127.44, 128.45, 134.26, 134.74, 137.98, 151.52, 156.51, 162.08 ppm.

2-Oxo-4-(p-tolyl)-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile 5e
Yield = 92%; M.p. > 300℃; IR (cm^{-1}) 3132 (NH), 2222 (C≡N), 1638 (C=O); ^{1}HNMR ($CDCl_3$): 2.32 (s, 3H, CH_3), 2.52-2.55 (m, 2H, CH_2), 2.76-2.79 (m, 2H, CH_2), 7.15–7.54 (m, Ar-CH, 8H), 13.12 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 12.54, 25.81, 28.71, 99.51, 118.21, 121.15, 126.41, 126.12, 127.32, 128.41, 129.42, 133.21, 135.76, 137.92, 152.52, 157.52, 162.10 ppm.

4-(4-Fluorophenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile 5f
Yield = 92%; M.p. > 300℃; IR (cm^{-1}) 3136 (NH), 2227 (C≡N), 1635 (C=O); ^{1}HNMR ($CDCl_3$): 2.50-2.53 (m, 2H, CH_2), 2.73-2.76 (m, 2H, CH_2), 7.16–7.57 (m, Ar-CH, 8H), 13.10 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 25.71, 27.71, 97.51, 119.21, 122.15, 124.42, 125.17, 127.31, 128.61, 129.32, 133.23, 134.76, 136.92, 152.52, 156.52, 163.10 ppm.

4-(Furan-2-yl)-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile 5g
Yield = 89 %; M.p. > 300℃; IR (cm^{-1}) 3136 (NH), 2227 (C≡N), 1635 (C=O); ^{1}H NMR ($CDCl_3$): 2.56-2.60 (m, 2H, CH_2), 2.63-2.66 (m, 2H, CH_2), 7.16–7.57 (m, Ar-CH, 6H), 12.10 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 24.41, 26.61, 98.52, 112.56, 119.21, 118.67, 122.35, 123.42, 124,67,125.17, 127.34, 128.65, 129.34, 134.23, 135.76, 136.92, 153.52, 157.52, 162.20 ppm.

2-Oxo-4-(thiophen-2-yl)-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile 5h
Yield = 88 %; M.p. > 300℃; IR (cm^{-1}) 3136 (NH), 2226 (C≡N), 1635 (C=O); ^{1}H NMR ($CDCl_3$) 2.57-2.61 (m, 2H, CH_2), 2.62-2.67 (m, 2H, CH_2), 7.18–7.55 (m, Ar-CH, 6H), 12.10 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 24.61, 25.74, 110.51, 114.45, 118.34, 119.21, 120.66, 122.15, 124.42, 125.17, 127.31, 128.61, 129.32, 133.23, 134.76, 136.92, 151.34, 152.52, 156.52, 162.20 ppm.

4-(1H-indol-2-yl)-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile 5i
Yield = 92%; M.p. > 300℃; IR (cm^{-1}) 3136 (NH), 2226 (C≡N), 1636 (C=O); ^{1}H NMR ($CDCl_3$) 2.57-2.61 (m, 2H, CH_2), 2.62-2.67 (m, 2H, CH_2), 7.18–7.55 (m, Ar-CH, 9H), 12.10 (bs, 1H, NH), 12.67 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 27.78, 28.91, 110.51, 114.21, 116.45, 119.56, 120.66, 122.15, 124.42, 125.17, 127.31, 128.61, 129.32, 133.23, 134.76, 135.44, 136.92, 140.33, 152.52, 156.52, 162.10 ppm.

RESULTS AND DISCUSSION

The FT-IR spectrum of the synthesised TiO_2 nanoparticles, bending vibrations due to the Ti–O–Ti band observed in the range of 500–600 cm^{-1}. The broad absorption band between 3400 and 3600 cm^{-1} indicates

the O–H stretching vibrations of surface –OH groups. Additionally, the band observed at 1626 cm^{-1} corresponds to the bending vibration of -OH groups[11] (Fig.-1a).

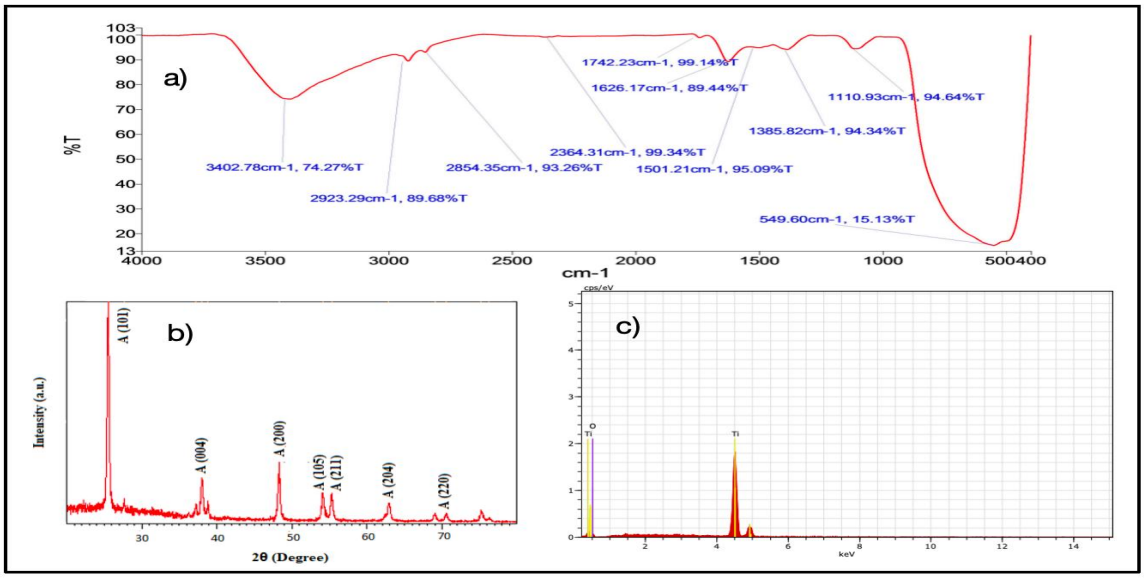


Fig.-1: (a) FT-IR Spectrum of Nano-TiO_2; b) X-ray Diffraction (XRD) Pattern of Nano-TiO_2; c) Energy Dispersive X-ray Analysis (EDX) of Nano-TiO_2

The XRD pattern of synthesised TiO_2 nanoparticles displayed seven distinct diffraction peaks at 2θ values of 7849°, 69.07°, 62.87°, 55.28°, 54.07°, 38.80° and 25.50°, corresponding to the (220), (204), (211), (105), (112), (004), (101), and crystal planes, respectively. These peaks are consistent with the standard JCPDS card no. 21-1272[12], confirming the formation of highly pure anatase-phase TiO_2 nanoparticles (Fig.-1b). The energy dispersive X-ray analysis study (EDX) shows the existence of titanium (Ti) and oxygen (O) (Fig.-1c). The SEM images of TiO_2NPs in different magnifications show that the whole structure is seen as pure, homogeneous and particles are agglomerated. Based on the TEM image, the particle diameter of the synthesised TiO_2 NPs was determined as approximately 20nm (Fig.-2a-b).

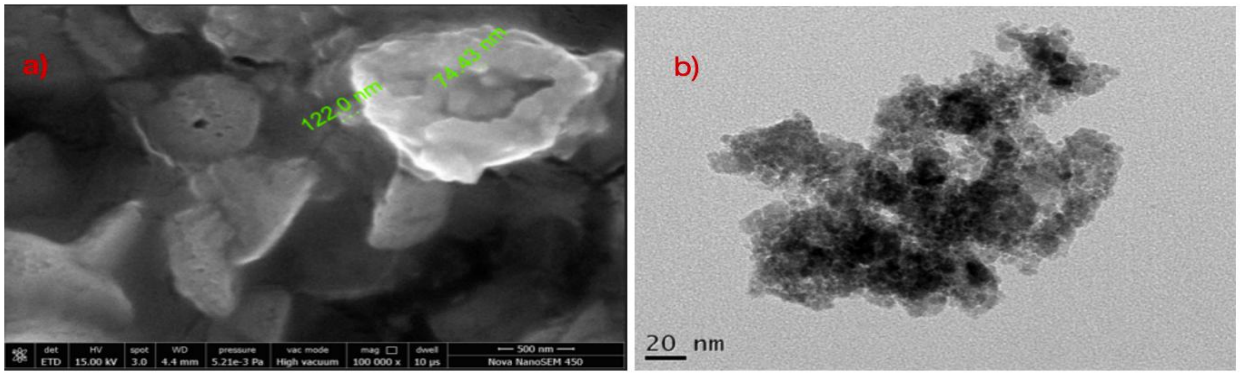


Fig.-2: (a) SEM Images of TiO_2 NPs; (b) TEM Images of TiO_2 NPs

The catalytic efficiency of the prepared TiO_2 NPs was investigated by choosing a model four-component reaction of benzaldehyde 1 (1mmol), malononitrile 2a (1 mmol), α-tetralone 3 (1 mmol), and ammonium acetate 4 (10 mmol), under sonication by choosing various reaction conditions and parameters for the synthesis of 2-amino-4-phenyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 5a (Table-1). Initially, the model reaction was performed under ultrasonic irradiation in an aqueous medium without a catalyst; however, only moderate conversion was observed, indicating the need for a catalyst (Table-1, entry 1). Hence, in order to enhance the reaction efficiency, we next examined the model reaction using green-synthesised TiO_2 nanoparticles under aqueous conditions (Table-1, entry-2).

The results revealed a significant improvement in product yield when TiO_2 NPs were used, highlighting their superior catalytic activity. For comparison, the reaction was also performed using commercially available TiO_2 (Table-1, entry-3), but the yield was notably lower than that obtained with the green-synthesised TiO_2 NPs. This can be attributed to the larger surface area and higher density of acidic reactive sites present in the nanoscale TiO_2 catalyst, which enhances its catalytic efficiency. The model reaction was carried out under sonication using various solvents such as acetonitrile (CH_3 CN) and ethanol, in the presence of nano-TiO_2 (Table-1, entries 4-5).

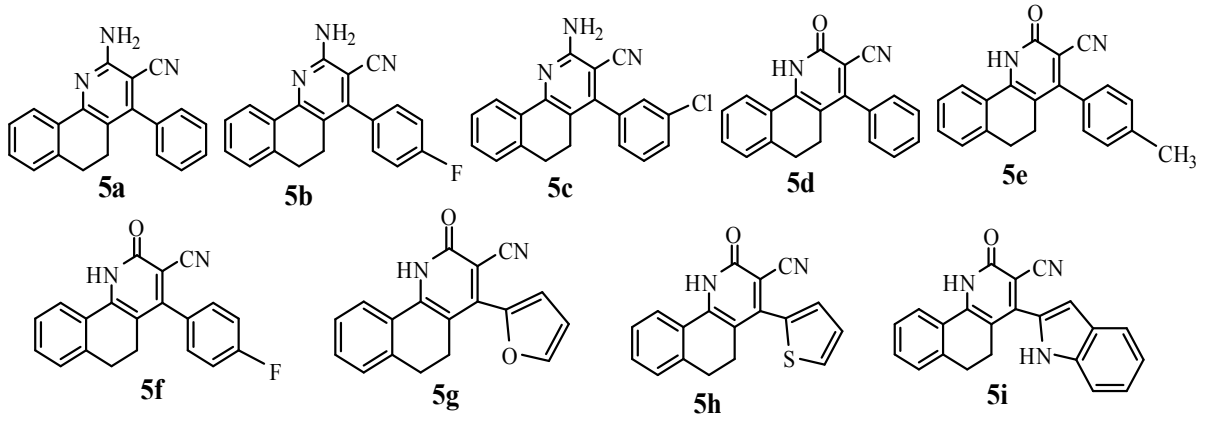
Table -1: The Optimisation of Reaction Conditions for the Synthesis of 5a[a]

S. No.	Catalyst (mol%)	Solvent	Time (min)	*Yield (%)
1.	Catalyst-free	H_2O	35	52
2.	Nano-TiO_2 (10 mol %)	H_2O	15	90
3.	Commercial TiO_2 (10 mol %)	H_2O	15	82
4.	Nano-TiO_2 (10 mol %)	CH_3CN	30	72
5.	Nano-TiO_2 (10 mol %)	CH_3OH	30	75
6.	Nano-TiO_2 (5 mol %)	H_2O	15	80
7.	Nano-TiO_2 (15 mol %)	H_2O	15	90

*Isolated Yield.

Among the solvents tested, water yielded the best results, making the approach more sustainable and environmentally friendly. The superior performance of water as a solvent under ultrasonic conditions can be explained by its high cavitation intensity, and the corresponding maximum temperature significantly influences sonochemical reactivity[13]. Hence, the use of TiO_2 NPs 10 mol % in aqueous medium under sonication is found best reaction conditions for the synthesis of the desired compound 5a. The use of smaller amounts of nano-TiO_2 (5 mol %) reduced the yield of 5a, and the larger amount of nano-TiO_2 (15 mol %) did not affect the product yield (Table-1, Entries 6–7).

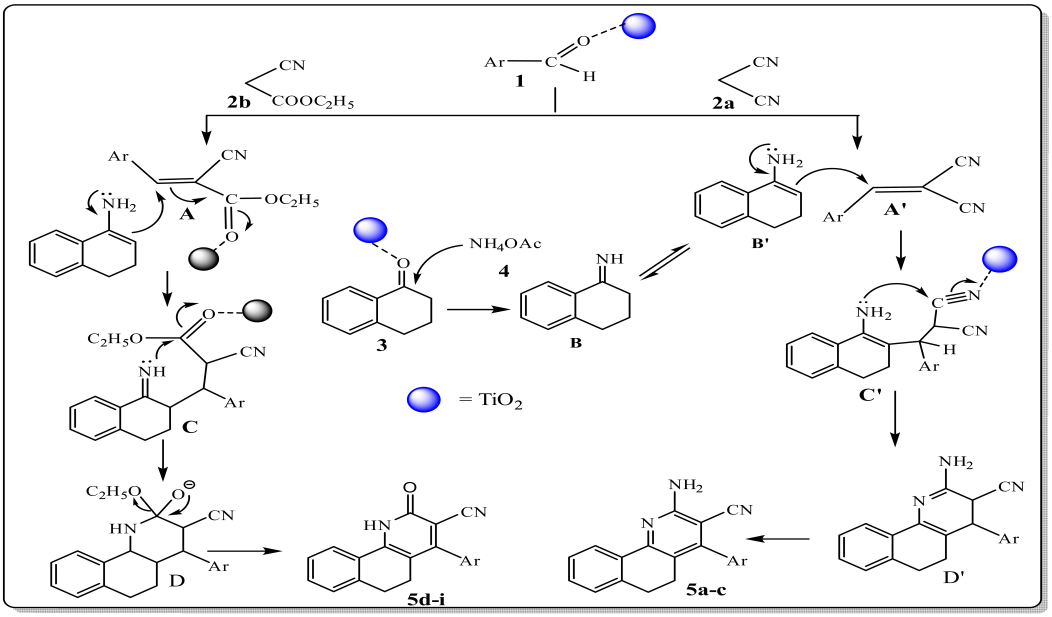
Table-2: Scope of Synthesis of benzoquinoline-carbonitriles 5a-i Catalysed by Green TiO_2 NPs



After choosing the best reaction conditions, the present multicomponent reaction was extended with other aromatic aldehydes and α-cyanoacetic ester 2b (R_2 = COOEt) (Table-2). The results show that the reaction proceeds smoothly with tested aromatic aldehydes and α-cyanoacetic ester to lead to the formation of corresponding, benzo[h]quinoline-3-carbonitriles **5a-i** in good yield under sonication using water as solvent and nano-TiO_2 as catalyst. In the plausible mechanism, nano-TiO_2 activates[14] the aromatioc aldehyde 1 and undergoes the Knoevenagel condensation with malononitrile 2a and ethylcyanoacetate 2b to give intermediate A and A′, respectively. Simultaneously, the TiO_2 enhanced the electrophilicity of carbonyl carbon of α-tetralone and attacked by ammonium acetate to give a enamine intermediate B or B′.

In the next step, TiO_2 catalysed Michael-type addition of intermediate B′ with Knoevenagel adduct A and A′ takes place, yielding intermediate C and C′, which subsequently undergoes intramolecular cyclisation

to form D and D′. After the intermediate D undergoes aromatization to form the 2-amino-4-phenyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile derivatives 5a-c and D′ undergoes elimination of a leaving group OC_2H_5 and aromatization to give the 2-oxo-4-phenyl-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile 5d-i (Scheme-2)



Scheme-2: The Proposed Mechanism for the Synthesis of Benzo[h]quinoline-3-carbonitriles 5a-i

CONCLUSION

In this paper, we have developed an efficient ultrasound-assisted synthetic protocol for the construction of benzo[h]quinoline-3-carbonitrile derivatives *via* a one-pot, four-component domino Knoevenagel-Michael condensation reaction catalysed by using biogenic TiO_2 nanoparticles in aqueous medium. This new approach offers several significant advantages, including excellent yield of product, shorter reaction times, simple work-up procedures, and catalyst recyclability. The nanocatalyst utilised in this study was synthesised via an eco-friendly route using *Raphanus sativus* leaf extract as a natural medium. This green synthesis approach enhances its significance as a sustainable and innovative strategy for modern catalytic process development.

ACKNOWLEDGEMENTS

We are thankful to the Malaviya National Institute of Technology (MNIT) Jaipur for the analyses and also thankful to Jaipur National University for financial assistance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

The present work is related to *SDG-9: Industry, Innovation, and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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Cite this article as: S. Sharma and R. Singh, *Rasayan J. Chem.*, 19(3), 1876-1882(2026), https://doi.org/10.31788/RJC.2026.1939720

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[RJC-9720/2026]