

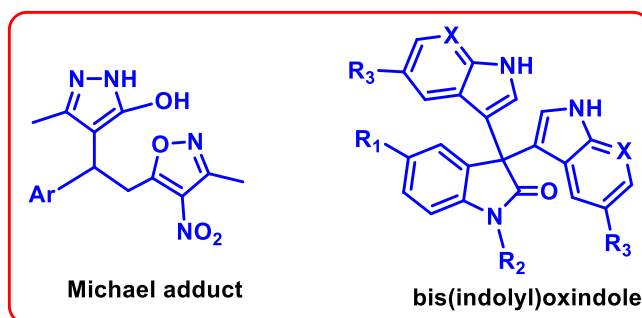


ENHANCING CATALYTIC EFFICIENCY: VTIO₂ NANOPARTICLES IN THE 1,6 MICHAEL ADDITION OF 3-METHYL-5-PYRAZOLONE TO 3-METHYL-4-NITRO-5-ALKENYL ISOXAZOLES FOR RAPID SYNTHESIS OF 3,3-BIS(INDOLYL)OXINDOLES IN PURE AQUEOUS MEDIUM

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Abstract

Herein, we present a report detailing the synthesis of column chromatography-free, heterogeneous vanadium doped titanium dioxide nanoparticles (VTiO₂ NPs) for catalysing the 1,6 Michael addition of 3-methyl-5-pyrazolone onto 3-methyl-4-nitro-5-alkenyl isoxazoles. Additionally, we report the swift synthesis of 3,3-di(indolyl)indolin-2-ones through the reaction of indole on isatin at room temperature in water, marking the first instance of such a process. The 1,6 Michael addition reaction yielded moderate to good yields, while the 3,3-bis(indolyl)oxindole products were obtained in quantitative yield.



Keywords: Vanadium doped Titanium dioxide nanoparticles (VTiO₂ NPs), 1, 6 – Michael addition, 3,3-di(indolyl)indolin-2-ones, green chemistry matrices, 3-methyl-4-nitro-5-alkenyl isoxazoles.

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Introduction

Heterogeneous catalysis has been instrumental in enabling chemists to develop environmentally friendly and cost-effective chemical processes ever since its inception. The industrial-scale adoption of this approach can be directly attributed to its introduction into chemical processes.¹ However, the pursuit of finding a versatile heterogeneous catalyst that can efficiently catalyse various reactions is often described as the "ideal" scenario, as it promises to reduce input costs and streamline the use of a single catalyst for multiple reactions. Incorporating nanoparticles has proven to be a significant advancement in enhancing the catalytic efficiency of heterogeneous catalysts. This is because the large surface area of nanoparticles promotes greater contact between reactants and catalyst, effectively emulating the performance of homogeneous catalysts.²

In this pursuit, researchers have developed a range of materials, including mesoporous materials, nanoparticles, and metal-organic frameworks (MOFs), to address this challenge. Among these materials, transition metal particles, whether in their native state or immobilized on various matrices, have gained recognition for their efficiency and cost-effectiveness as catalysts.³ Titanium dioxide (TiO_2), in particular, is a well-established additive in the food and cosmetic industries. Both native-state TiO_2 nanoparticles and functionalized variants are known for their ability to catalyse processes such as photodegradation⁴ and a variety of other organic reactions.⁵ Unfunctionalized TiO_2 nanoparticles (TiO_2 NPs)⁶ are characterized by low toxicity.⁷ In addition to this, vanadium doped TiO_2 nanoparticles displayed greater catalytic activity for diverse chemical transformations.⁸⁻¹⁰ Hence, a comprehensive investigation into the catalytic efficacy of vanadium-doped titanium dioxide nanoparticles (VTiO_2 NPs) in facilitating a range of reactions within the established optimal parameters is expected to play a pivotal role in furthering researchers' endeavors towards attaining sustainability objectives.

Conversely, water has gained widespread recognition as a solvent for a broad spectrum of organic reactions, encompassing organometallic reactions,¹¹ pericyclic reactions,¹² and various other synthetic processes.¹³ Existing literature strongly indicates that the utilization of heterogeneous catalytic methods in aqueous media can pave the way for more environmentally friendly, cost-effective, and dependable chemical operations on a larger scale.¹⁴

These observations have guided our research focus toward addressing the challenge of conducting various types of reactions using the same catalyst in an aqueous environment. This work is part of our ongoing research efforts aimed at devising strategies for multicomponent reactions and sustainable protocols for the synthesis of biologically active compounds.¹⁵ Dwivedi and his research team introduced a novel approach by utilizing heterogeneous titanium dioxide nanoparticles (TiO_2 NPs) as a catalyst, eliminating the need for column chromatography. They applied this catalyst to facilitate the 1,6 Michael addition of 3-methyl-5-pyrazolone onto 3-methyl-4-nitro-5-alkenyl isoxazoles and achieved the rapid synthesis of 3,3-di(indolyl)indolin-2-ones through the reaction of indole with isatin. Notably, these reactions were performed in water at room temperature, marking the first time such a method has been demonstrated.¹⁶

In this context, we present what we believe to be the initial report on the utilization of vanadium doped titanium dioxide nanoparticles (VTiO_2 NPs) as a catalyst for the 1,6 Michael addition of 3-Methyl-5-pyrazolone on 3-methyl-4-nitro-5-alkenyl isoxazoles and the rapid synthesis of 3,3-di(indolyl)indolin-2-ones, all conducted in water. Notably, in both cases, the products were obtained in pure form and in quantitative yields without the need for column chromatography.

Results and discussion

Synthesis and characterization of TiO_2 NPs and VTiO_2 NPs

20 mL of Tetra-n-Butyl Ortho Titanate and 40 mL of $\text{C}_2\text{H}_5\text{OH}$ should be added to make up of Solution- 1 and agitated for 10 minutes in a 150 mL Pyrex glass beaker. Next, gradually add 3.2 mL of Nitric acid while stirring for 30 minutes. In a 150 ml Pyrex glass beaker, Solution - 2 was made by dissolving the required quantity of 5 wt. % of NH_4VO_3 dopant in a 40 mL of $\text{C}_2\text{H}_5\text{OH}$ and 7.2 mL of H_2O . The mixture was then agitated for 30 minutes. Sol was generated by adding Solution-2 to Solution-1 drop by drop while stirring frequently. The produced sol was kept in dark for 48 hours to form a gelation, which was then dried for 24 hours at 75°C and the crystals were ground for 4 to 6 hours to a fine size. The fine powder that had been obtained was then calcined in a muffle furnace for 5 hours at 450°C . The fine powder was collected and grounded, and placed in airtight amber colour vials. TiO_2 was produced using the same process without addition of dopants.¹⁷ Analytical data confirms the TiO_2

NPs and VTiO_2 NPs formation for the study (Figure 1a-e). The powder XRD (Figure 1a) clearly depicts characteristic peaks at (101), (004), (200), (105), (211), (204), (116), (220) and (215) corresponds to anatase phase of TiO_2 NPs & VTiO_2 NPs and compared with standard (JCPDS card no. 21-1272). FESEM images of TiO_2 NPs

and VTiO_2 NPs indicate the uniform size and spherical shape of the particles (Figure 1b & 1c) and the EDS (energy dispersive X-ray spectroscopy) spectrum of synthesized TiO_2 NPs and VTiO_2 NPs confirms the presence of Ti and O (Figure 1d & 1e).

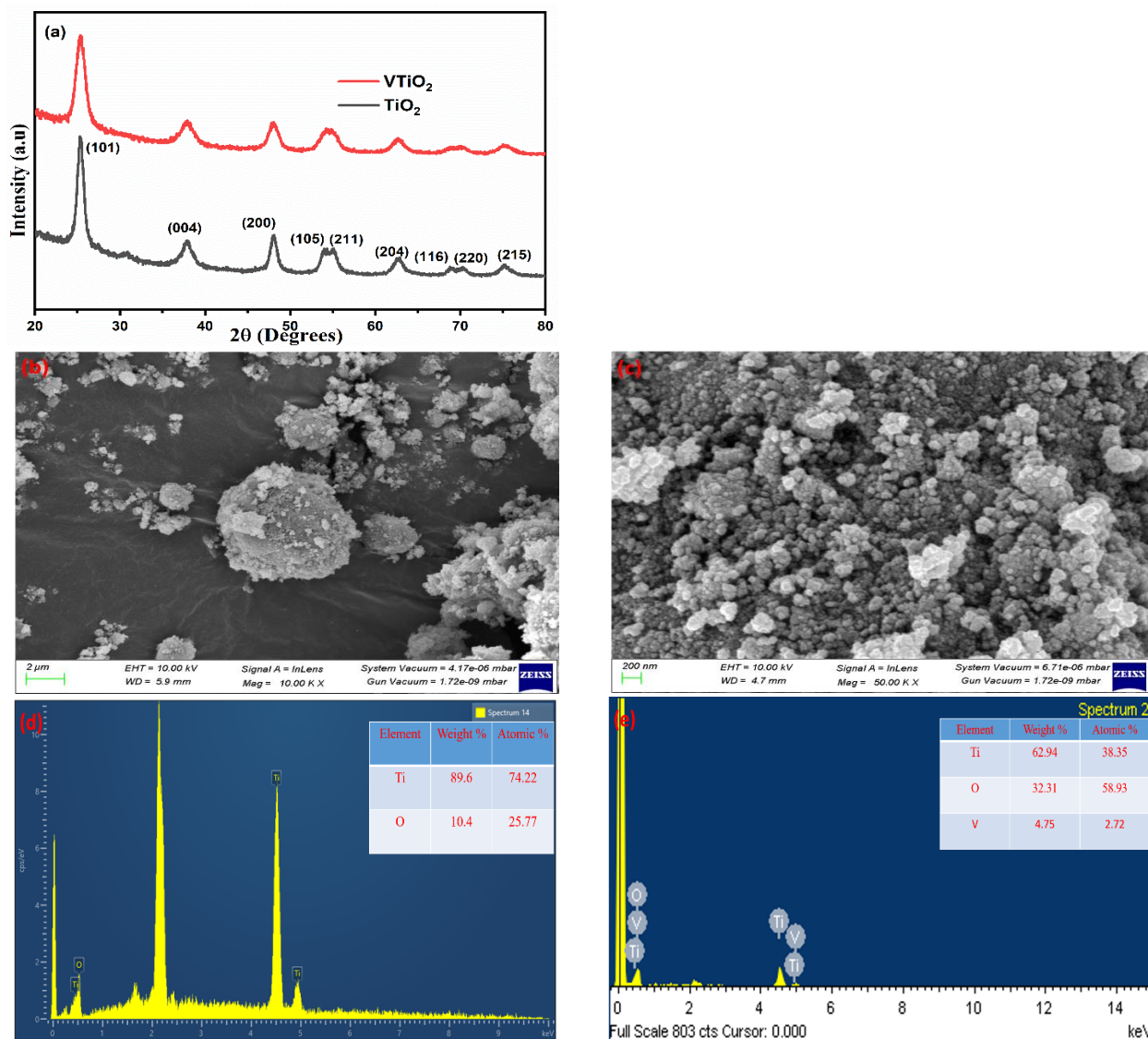


Figure 1; Characterisations of TiO_2 NP and VTiO_2 NP Catalyst; **1a)** powder XRD with the simulated graph (JCPDS Card no. 21-1272). **1b)** FESEM image of TiO_2 , **1c)** FESEM image of VTiO_2 **1d)** EDS elemental analysis of TiO_2 , **1e)** EDS elemental analysis of VTiO_2

Optimisation and substrate scope studies

Optimization investigations were initially conducted for the 1,6 Michael addition of 3-methyl-5-pyrazolone (2) to 3-methyl-4-nitroisoxazole alkenes (1a). This exploration involved the utilization of different water-stable Lewis acids and EtOH as a solvent. Our aim was to comprehend the efficiencies of catalysts in environmentally friendly conditions under open-air settings (Figure 2a).

As evident from the observations, the application of Lewis acid catalysis proved to be productive, yielding 40% with a 10 mol% concentration of $\text{Sc}(\text{OTf})_3$ as a catalyst within 90 minutes. The introduction of $\text{Cu}(\text{OTf})_2$ during the same timeframe reduced the yield to 21%, while $\text{Fe}(\text{OTf})_3$ enhanced it to 51%. Contrarily, the use of 10 mol% commercial TiO_2 solid yielded only 45% within the same time frame. However, employing 10 mol% TiO_2 NPs in ethanol resulted

in a significantly improved yield of 82% within the 90-minute duration. The vanadium-doped titanium dioxide nanoparticles (VTiO_2 NPs) catalyst demonstrated a 96% product yield within

the anticipated timeframe, surpassing the yield achieved by titanium dioxide nanoparticles (TiO_2 NPs) as a catalyst.

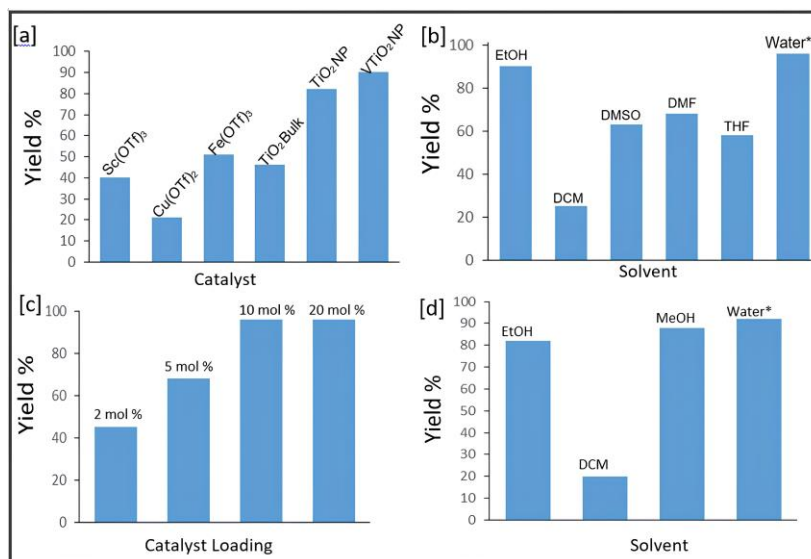


Figure 2: ^aReaction conditions: unless otherwise specified, **Figure 2a-c** represents the optimization studies are carried out on the reaction with 3-methyl-4-nitroisoxazole alkenes (**1a**) (1.0 mmol), 3-methyl-5-pyrazolone (**2**) (1.0 mmol) at room temperature. **Figure 2d** represents the solvent optimization for 3,3-bis(indolyl)oxindoles synthesis carried out on the reaction with isatin (**4a**) (1.0 mmol), indole (**5a**) (2.0 mmol) and 10 mol% VTiO_2 NPs at room temperature. ^b Isolated yields.

Figure 2a: Catalyst optimization in ethanol solvent with a standard reaction time of 90 min.

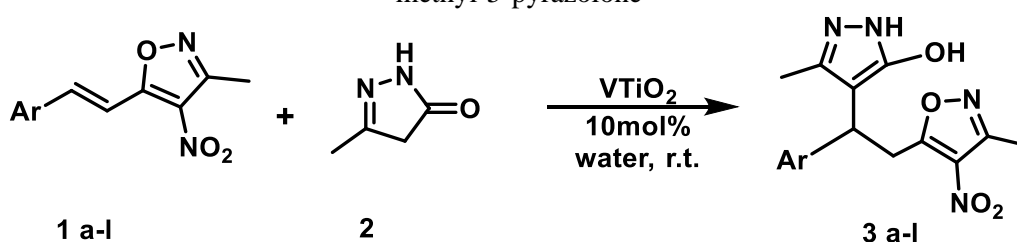
Figure 2b: Solvent optimization with 10 mol% VTiO_2 NPs and standard reaction time of 90 min.*Reaction completed in 60 min.

Figure 2c: Catalyst loading optimization in water solvent with a standard reaction time of 60min.

Figure 2d: Solvent optimization for 3,3-bis(indolyl)oxindoles synthesis with 10 mol% VTiO_2 NPs and standard reaction time of 60 min.*Reaction completed in 15 min.

Further optimization studies were conducted to enhance yield and reduce reaction time (**Figure 2b**). Various solvents were explored for the catalytic reaction, revealing that water yielded an impressive 96% within 60 minutes, outperforming all other organic solvents (**Figure 2b**). Subsequent investigations focused on the impact of catalyst loading (**Figure 2c**), revealing that 10 mol% was the optimal amount for achieving complete reaction in water. Below 10%, the catalyst loading proved inefficient, while an increase to 20 mol% did not significantly improve yield or reduce reaction time. Consequently, we determined that water with a 10 mol% catalyst loading represented the optimized conditions for the 1,6 Michael addition reaction of 5-methylpyrazolone on 3-methyl-4-nitroisoxazole alkenes in pure water. These optimized conditions demonstrated versatility across a broad substrate scope, yielding favorable results (**Table 1**).

Table 1. Substrate scope for 1,6 Michael addition reaction of 3-methyl-4-nitroisoxazole alkenes and 3-methyl-5-pyrazolone



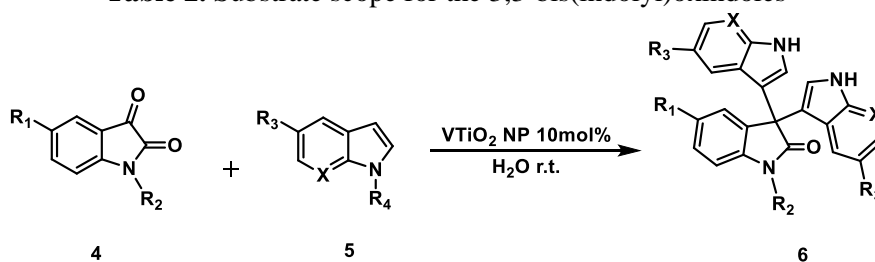
Entry ^a	Ar	2	Product	Time (hrs)	Yield (%) ^b
1	1a= C ₆ H ₅	2a	3a	1.5	86
2	1b: 3-F-C ₆ H ₅	2a	3b	2.0	96
3	1c: 4-F-C ₆ H ₅	2a	3c	1.0	89
4	1d: 2-Cl-C ₆ H ₅	2a	3d	1.2	84
5	1e: 4-Cl-C ₆ H ₅	2a	3e	1.3	88
6	1f: 2-Br-C ₆ H ₅	2a	3f	1.5	87
7	1g: 4-Br-C ₆ H ₅	2a	3g	1.5	84
8	1h: 4-NO ₂ -C ₆ H ₅	2a	3h	2	89
9	1i: 4-Me-C ₆ H ₅	2a	3i	1	86
10	1j: 4-OMe-C ₆ H ₅	2a	3j	1	89
11	1k= furan	2a	3k	1.5	87
12	1l= thiophene	2a	3l	1	89

^a Reaction conditions: unless otherwise specified, the reaction was carried out with 3-methyl-4-nitroisoxazole alkenes (**1a-l**) (1.0 mmol), 3-methyl-5-pyrazolone (**2**) (1.0 mmol) and VTiO₂ NPs (10 mol%) in 3 mL H₂O. Isolated yields of the product (**3a-l**).

We further explore the diversity of the catalytic application of VTiO₂ NPs by synthesizing 3,3-bis(indolyl)oxindoles in neat water. Though bis(indolyl)methane synthesis using aromatic aldehydes and indoles is well established with a range of Lewis acid catalysts¹⁸ 3,3-bis(indolyl)oxindoles synthesis by reacting isatin with indoles in water at room temperature is less explored¹⁹. As it can be seen from the optimization study (**Figure 2c**), water has given quantitative yield in 15 minutes using **4a** and **5a**

as model substrates with 10 mol% of VTiO₂ NPs catalyst loading (**Figure 2c**), without any change from previous optimized condition. Other organic solvents performed poorly compared to neat water medium giving less than 80% after 90 minutes (**Figure 2c**). With these optimized conditions in hand, we explored the substrate scope and found that, the developed protocol was efficient and accommodated an array of substrates, giving quantitative yields within a maximum of 20 minutes reaction time (**Table 2**). However, few interesting observations were made; the reaction did not proceed in case of 5-CN indole was used (**Table 2, entry 16**) and Azo indole (**Table 2, entry 17**). N-methyl Indole too failed to give the desired product (**Table 2, entry 18**).

Table 2. Substrate scope for the 3,3-bis(indolyl)oxindoles



Entry ^a	Product	R ₁	R ₂	R ₃	R ₄	X	Time (min)	Yield (%) ^b
1	6a	H	H	H	H	CH	15	98
2	6b	F	H	H	H	CH	10	97
3	6c	Cl	H	H	H	CH	10	96
4	6d	Br	H	H	H	CH	15	98
5	6e	NO ₂	H	H	H	CH	20	95
6	6f	H	C ₃ H ₅	H	H	CH	20	96
7	6g	H	CH ₂ -Ph	H	H	CH	15	97
8	6h	OMe	H	H	H	CH	20	98
9	6i	H	H	Br	H	CH	15	97
10	6j	F	H	Br	H	CH	10	96
11	6k	Cl	H	Br	H	CH	12	96
12	6l	NO ₂	H	Br	H	CH	15	98
13	6m	H	C ₃ H ₅	Br	H	CH	18	97

14	6n	H	CH ₂ -Ph	Br	H	CH	20	96
15	6o	OMe	H	Br	H	CH	20	94
16	6p	H	H	CN	H	CH	60	-*
17	6q	H	H	H	H	N	60	-*
18	6r	H	H	H	Me	CH	60	-*

^a Reaction condition: unless otherwise specified, the reaction was carried out with isatins (**4a-i**) (1.0 mmol), indole (**5a-d**) (2.0 mmol) and VTiO₂ NPs (10 mol%) in 3 mL H₂O was stirred. Isolated yields of the product (**6a-r**).^b Isolated yield * no product was formed and starting material was recovered.

Plausible Mechanism

Regarding the 1,6 Michael addition, the 3-methyl-5-pyrazolone exhibits keto-enol tautomerism. Notably, the presence of water on the VTiO₂ catalyst surface facilitates robust hydrogen bonding with the substrates, immobilizing them and bringing the reactants into close proximity.¹⁶ For the synthesis of 3,3-bis(indolyl)oxindoles, our rationale involves the stepwise addition of indole to isatin. The initial addition is succeeded by the dehydration of the isatin-indole adduct, leading to the formation of a reactive alkylideneindolenine,²⁰ and this intermediate promptly undergoes further indole addition, resulting in the formation of the bis indole product.

Experimental section

General experimental details

All commercially available chemicals were used without further purification. ¹H NMR spectra were obtained on Bruker 500 MHz FT-NMR spectrometers. ¹³C NMR spectra were recorded at 125 MHz. Chemical shifts are reported in relative to the TMS signal. Multiplicity is indicated as follows: s (singlet); bs (broad singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets), etc. The hydrodynamic sizes of the synthesized TiO₂ NPs were measured using a DLS instrument (MicrotracZetatrax, U2771). FT-IR spectrometer (Shimadzu) in the range of 400–4000 cm⁻¹. Vanadium doped titanium dioxide nanoparticles (VTiO₂ NPs) was synthesized as per literature procedure. VTiO₂ phase was verified by X-ray diffraction (XRD) analysis were carried out at room temperature using a Bruker D8 Advance X-ray diffractometer. Elemental analysis and imaging were performed using EDS Nova Nano SEM-450 using a scanning electron microscope (SEM) equipped with EDS.

General Procedure for 1, 6 Michael addition of 3-methyl-5-pyrazolone on 3-methyl-4-nitroisoxazole alkenes (3a-l)

To a solution of 3-methyl-4-nitroisoxazole alkenes (**1a-1l**) (1 mmol) in water (3.0 mL) was added 3-methyl-5-pyrazolone (**2**) (1 mmol) and VTiO₂NPs (0.1 mmol, 10 mol%) and the resulting mixture was stirred for the specified duration (**Table 1**) at room temperature. Progress of the reaction was determined by thin layer chromatography (TLC). Upon completion, the solid crude product was filtered and dried. The obtained solid was dissolved in ethyl acetate and subjected to centrifugation at 15000 rpm for 1 hour to separate the catalyst nanoparticles. The organic layer was then passed through a celite bed to eliminate any particulate impurities from the product, followed by concentration under reduced pressure. The resulting crude material was recrystallized from methanol to yield the analytically pure product (**3a-l**).

Spectral data for selected compounds of 1, 6 Michael addition reaction (3a, 3b, 3i and 3l):

5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)-4H-pyrazol-3-ol, 3a: M.P.: 191-193 °C. IR (KBr) ν_{\max} (cm⁻¹) 3412, 2928, 2860, 1604, 1528, 1420, 1221, 832, 749, 651, 525; ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.1 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 4.46 (t, *J* = 8.3 Hz, 1H), 4.19 (dd, *J* = 15.1, 9.5 Hz, 1H), 3.94 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.49 (s, 3H), 2.12 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 178.81, 165.40, 159.99, 148.02, 142.50, 134.95, 133.23, 132.10, 131.37, 106.38, 42.72, 37.36, 16.37, 15.05. HRMS (ESI+): *m/z* calculated for C₁₆H₁₆N₄O₄ [M+H]⁺: 329.1250; found: 329.1250.

4-(1-(3-fluorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)-5-methyl-4H-pyrazol-3-ol, 3b: M.P.: 193-195 °C. IR (KBr) ν_{\max} (cm⁻¹) 3425, 2932, 2877, 1609, 1557, 1420, 1223, 825, 756, 632, 519; ¹H NMR (500 MHz, CDCl₃) δ 7.26 – 7.21 (m, 1H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.90 (t, *J* = 8.4 Hz, 1H), 4.41 (t, *J* = 8.2 Hz, 1H), 4.15 (dd, *J* = 15.3, 9.3 Hz, 1H), 3.90 (dd, *J* = 15.4, 7.2 Hz, 1H), 2.50 (s, 3H), 2.12 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 179.06, 169.01, 167.16, 165.19, 160.22, 152.12, 150.13, 143.99, 134.89, 127.90, 118.43, 118.26, 105.16, 42.41, 37.29, 17.08,

15.16. HRMS (ESI+): m/z calculated for $C_{16}H_{15}FN_4O_4$ [M+H]⁺: 347.1156; found: 347.1169. **5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(p-tolyl)ethyl)-4H-pyrazol-3-ol, 3i**: M.P. 203-205 °C. IR (KBr) ν_{max} (cm⁻¹) 3346, 2931, 2867, 1605, 1498, 1475, 1272, 832, 756, 659, 568; ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 4.40 (t, J = 8.1 Hz, 1H), 4.13 (dd, J = 15.3, 9.2 Hz, 1H), 3.89 (dd, J = 15.4, 7.1 Hz, 1H), 2.49 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 178.78, 165.43, 159.87, 146.08, 143.18, 141.52, 135.87, 133.76, 131.85, 106.45, 42.44, 36.59, 26.17, 16.56, 15.19. HRMS (ESI+): m/z calculated for $C_{17}H_{18}N_4O_4$ [M+H]⁺: 343.1406; found: 343.1433. **5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(thiophen-2-yl)ethyl)-4H-pyrazol-3-ol, 3l**: M.P. 228-230 °C. IR (KBr) ν_{max} (cm⁻¹) 3389, 3012, 2764, 1604, 1525, 1464, 1262, 827, 725, 624, 554; ¹H NMR (500 MHz, CDCl₃) δ 7.17 (d, J = 4.8 Hz, 1H), 6.98 (s, 1H), 6.89 (d, J = 3.6 Hz, 1H), 4.74 (s, 1H), 4.13 (d, J = 9.2 Hz, 1H), 4.03 (d, J = 7.0 Hz, 1H), 2.50 (s, 3H), 2.17 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 179.06, 165.04, 161.32, 153.12, 136.11, 130.65, 129.09, 106.17, 38.28, 37.58, 16.45, 15.34. HRMS (ESI+): m/z calculated for $C_{14}H_{14}N_4O_4S$ [M+H]⁺: 335.0814; found: 335.0824.

General Procedure for the synthesis 3,3-bis(indolyl)oxindoles (6a-r)

In a water solution containing isatins (1 eq.) and VTiO₂ NPs (10 mol%) at a ratio of 3 mL/mmol, indoles (1 eq.) were introduced and stirred for the specified duration at room temperature (see Table 2). The progression of the reaction was monitored through TLC, with the disappearance of isatin color and the formation of white solid serving as visual indicators. Upon completion of the reaction, as evidenced by TLC, the reaction mixture was filtered, yielding a white solid crude product. This solid was then dissolved in ethyl acetate and subjected to centrifugation for 1 hour at 15000 rpm to isolate nanoparticles. The organic layer was subsequently passed through a celite bed to eliminate any particulate impurities, followed by concentration under reduced pressure. The resulting crude material underwent recrystallization from methanol, resulting in the isolation of analytically pure 3,3-di(indolyl)indolin-2-ones products (6a-r).

Spectral data for selected compounds of 3,3-bis(indolyl)oxindoles (6a, 6f, 6k):

[3,3':3',3''-terindolin]-2'-one, 6a: White solid, M.P. 253-255 °C. IR (KBr, cm⁻¹) 3425, 3427, *Eur. Chem. Bull.* **2021**, 10(Regular Issue 4), 350–358

3156, 3078, 1703, 1614, 1497, 1017, 813 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.29 (s, 1H), 7.42 (d, J = 3.8 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.94 – 6.92 (m, 1H), 6.87 (dd, J = 14.7, 7.4 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 182.78, 142.78, 132.12, 130.54, 129.46, 129.47, 126.32, 125.99, 123.41, 119.54, 116.24, 114.61, 56.98. HRMS (ESI+): m/z calculated for $C_{24}H_{17}N_3O$ [M+H]⁺: 364.1450; found: 364.1496.

1'-allyl-[3,3':3',3''-terindolin]-2'-one, 6f: White solid, M.P. 252-254 °C. IR (KBr, cm⁻¹) 3398, 3371, 3202, 30439, 1664, 1611, 1463, 1110, 767 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.08 (s, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.38 (t, J = 9.2 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.4 Hz, 2H), 6.89 (t, J = 7.5 Hz, 1H), 5.98 – 5.84 (m, 1H), 5.33 – 5.16 (m, 1H), 4.49 (d, J = 4.5 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 146.90, 141.92, 139.05, 138.95, 136.93, 136.46, 132.59, 130.79, 129.31, 127.17, 126.04, 125.85, 123.52, 123.42, 122.35, 122.26, 119.29, 119.26, 116.39, 116.36, 113.82, 57.44, 47.13. HRMS (ESI+): m/z calculated for $C_{27}H_{21}N_3O$ [M+H]⁺: 404.1763; found: 404.1836.

5,5''-dibromo-5'-chloro-[3,3':3',3''-terindolin]-2'-one, 6k: White solid, M.P. 288-291 °C. IR (KBr, cm⁻¹) 3647, 3564, 3379, 3032, 1703, 1613, 1605, 1478, 1086, 797, 748 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.76 (s, 2H), 10.55 (s, 1H), 7.45 (s, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.09 (s, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.89 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 183.43, 144.86, 140.92, 140.72, 132.34, 132.28, 131.75, 130.92, 128.84, 129.93, 127.89, 126.89, 127.95, 118.78, 116.77, 116.45, 57.49. HRMS (ESI+): m/z calculated for $C_{24}H_{14}Br_2ClN_3O$ [M+H]⁺: 553.9270; found: 553.9294.

Conclusion

In conclusion, we present the catalytic prowess of VTiO₂ NPs in facilitating the 1,6 Michael addition of 3-methyl-5-pyrazolone on 3-methyl-4-nitro-5-alkenyl isoxazoles and the rapid synthesis of 3,3-di(indolyl)indolin-2-ones. Notably, these reactions were conducted in pure water at room temperature, marking a new achievement. The efficacy of this heterogeneous catalytic approach was demonstrated through successful scale-up experimentation (10 mmol), and recyclability trials for both reactions were conducted for up to four cycles.

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Reference

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