

Nano-TiO₂: A novel, efficient and recyclable catalyst for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles in solvent-free conditions

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ABSTRACT

A convenient and efficient one-pot four-component synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using nano TiO₂ as a recyclable catalyst is reported. The results show that the methodology has several advantages such as low loading of catalyst, excellent yield, short reaction time, operational simplicity and solvent-free conditions.

Keywords: Nano TiO₂, Tetrasubstituted imidazoles, Solvent-free conditions, Reusable catalyst.

1. INTRODUCTION

Imidazoles are very important compounds with wide spectrum of biological activities such as anti-inflammatory [1], anti-allergic [2], anti-bacterial [3], anti-tumor [4], and plant growth regulators [5], activities. Furthermore, they act as glucagon receptors [6]. Recent advances in green chemistry and organometallic catalysis has extended the application of imidazoles as ionic liquids [7], and N-heterocyclic carbenes [8].

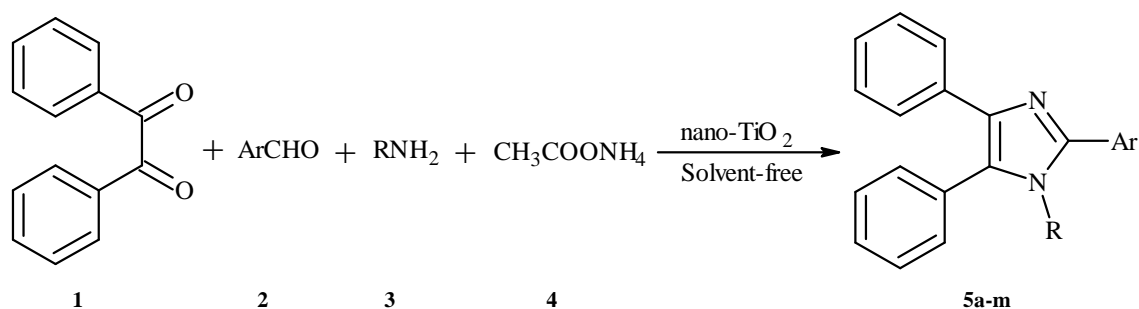
The design and development of Multi-component reactions (MCRs) for the generation of heterocycles receive growing interest [9a, b]. One example of MCRs is four-component, one-pot synthesis of tetra substituted imidazoles. In view of different biological and chemical applications of imidazoles, the development of suitable synthetic methodologies for their generation has been a topic of great

interest in recent times. The general method involves four component condensation of 1,2-diketones, aromatic aldehydes, primary amines and ammonium acetate in the presence of various catalysts, such as zinc oxide [10], carbon-based solid acid [11], Bronsted acidic ionic liquid [12], silica gel/NaHSO₄ [13], K₅CoW₁₂O₄.3H₂O [14], BF₃-SiO₂ [15], Molecular iodine [16], HClO₄-SiO₂ [17], and L-proline [18]. In addition, they can also be accessed by the condensation of a 1, 2-diketone with an aryl nitrile and primary amine under microwave irradiation [19], cyclo-addition reaction of mesoionic 1, 3-oxazolium-5-olates with N-(aryl-methylene)-benzenesulfonamide [20], and N-(2-oxo) amides with ammonium trifluoroacetate [21]. However, in spite of their potential utility, some of the reported methods suffer from certain drawbacks such as expensive reagents, harsh conditions,

use of toxic catalysts and organic solvents that are harmful to environment, and moderate yields. Therefore, to avoid these limitations, there is still a need for the development of a new protocol for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles in terms of operational simplicity, reusability of the catalyst, highyielding, and economic viability.

Recently, metal nanoparticles have attracted a great attention as heterogeneous catalysts because of their interesting structure and high catalytic activities [22a, b]. In particular, magnetite nanoparticles have emerged as one of the most useful heterogeneous catalysts due to their numerous applications in bio-technology and medicine [23a, b]. Of these, TiO₂ nanoparticles are the most promising

catalysts because of their ease of handing, ease of recovery, high catalytic activities, and reactivates in various organic transformations [24a, b]. However, there are no reports on the use of TiO₂ nanoparticles for one-pot four-component synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles. In continuation of our previous works on the applications of reusable catalysts in the synthesis of heterocyclic compounds [25a-c], in this article, we report nano-TiO₂ as a highly efficient clean and economically valuable catalyst for the one-pot, four-component synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles **5a-m** from reaction of benzil **1**, aromatic aldehydes **2**, primary amines **3**, and ammonium acetate **4** under solvent-free conditions (Scheme 1).



Scheme 1: Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles **5a-m** using nano-TiO₂ as catalyst.

2. EXPERIMENTAL

All reagents were purchased from Merck Fine Chemicals and were used without further purification. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained using 4300 Shimadzu spectrophotometer as KBr disks. The ¹H NMR, 400MHz spectra were recorded with a Bruker DRX 400 spectrometers.

2.1 General procedure for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles

A mixture of benzil (1mmol), aromatic aldehydes (1mmol), primary amine (1mmol), ammonium acetate (1mmol), and nano-TiO₂ (0.20 mmol) was heated on the oil bath at 110°C for 45 min. The reaction was monitored by TLC using n-hexane-Ethyl acetate (5:2) as an eluent. After completion of the reaction, the reaction mixture was cooled to room temperature, ethanol 95% was added and the mixture was

heated for 5 min. After cooling the mixture to room temperature, the TiO₂ nanoparticles were filtered and the crude product was collected and recrystallized from ethanol to give compounds **5a-m** in high to excellent yields. All products were known and characterized by comparison of their physical and spectroscopic data with those of reported techniques.

2.2 Reusing of the catalyst

The recyclability of the catalyst in the reaction of benzil, benzaldehyde, aniline, ammonium acetate in the presence of nano TiO₂ was checked. The separated catalyst can be reused after washing triple with ethanol 95%, drying at 90 °C and reused in another reaction. It showed the same activity as fresh catalyst without any loss of its activity after seven times (Table 3).

2.2.1 2-(4-Chlorophenyl)-1-(4-nitrophenyl)-4, 5-diphenyl-1H-imidazole (5g)

m.p. 168-169 °C; IR (cm⁻¹, KBr): 3100, 1530, 1475, 1350; ¹H NMR (DMSO-d₆ 400 MHz) δ: 6.70-7.74 (m, 18H, ArH); ¹³C NMR (DMSO-d₆ 100 MHz) δ: 146.40, 137.53, 137.58, 134.88, 134.26, 131.19, 131.17, 130.67, 130.56, 130.14, 129.37, 129.26, 129.23, 128.45, 127.56, 126.74, 126.48, 126.28 .

2.2.2 1-Benzyl-2-(4-nitrophenyl)-4, 5-diphenyl-1H-imidazole (5h)

m.p. 165-167 °C ; IR(cm⁻¹, KBr): 3108, 1528, 1474, 1355; ¹H NMR (DMSO-d₆

400 MHz) δ: 5.44 (s, 2H, CH₂), 6.70-8.36 (m, 19H, ArH); ¹³C NMR-(DMSO-d₆ 100 MHz) δ: 147.58, 145.15, 138.38, 137.22, 137.28, 134.56, 132.16, 131.45, 130.66, 129.23, 129.65, 129.45, 129.23, 129.37, 129.31, 128.57, 127.76, 127.21, 126.57, 126.35, 126.09, 124.72.

2.2.3 2-(4-Methoxyphenyl)-1, 4, 5-triphenyl-1H-imidazole (5k)

m.p. 155-159 °C; IR(cm⁻¹, KBr): 3124, 1470; ¹H NMR (DMSO-d₆ 400 MHz) δ: 3.70 (s, 3H, CH₃), 6.81-7.53 (m, 19H, ArH); ¹³C NMR(DMSO-d₆ 100 MHz) δ: 159.54, 146.44, 137.33, 137.12, 134.87, 131.61, 131.22, 131.24, 130.22, 129.66, 129.26, 129.18, 128.92, 128.61, 128.68, 126.54, 126.77, 123.28, 114.28, 55.52.

3. RESULTS AND DISCUSSION

Initially, nano TiO₂ powder was easily prepared according to the reported procedure. Figure 1 shows the XRD patterns of prepared nano TiO₂ powder. Transmission Electron Microscopy (TEM) analysis was used for characterization of nano TiO₂ powder (Figure 2). The TEM image reveals the spherical nano TiO₂ powder with average size 20-30 nm. SEM image of the nanoparticles prepared is shown in Figure 3.

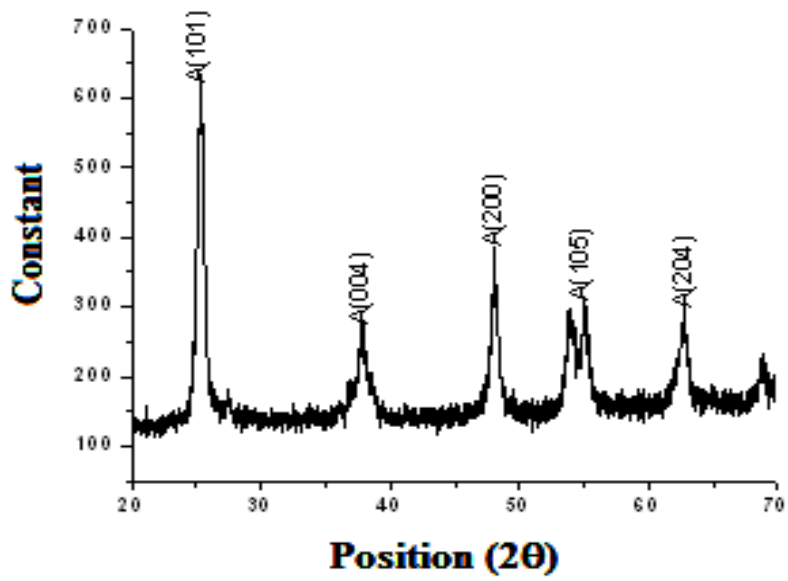


Fig. 1. The X-ray diffraction patterns of the nano TiO₂

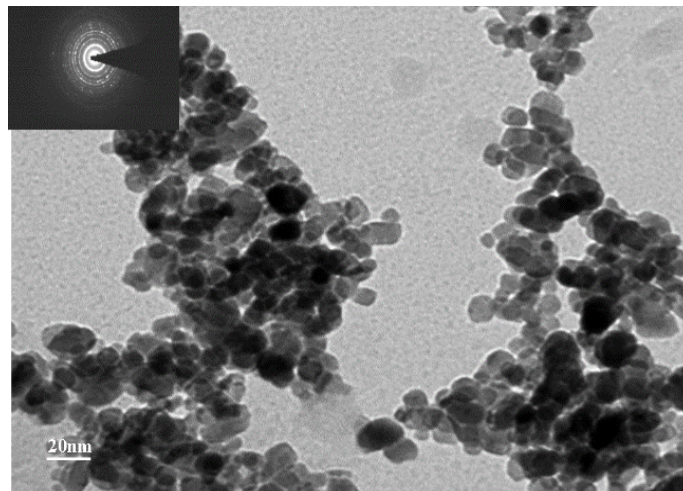


Fig. 2. TEM images of TiO₂ nanoparticles

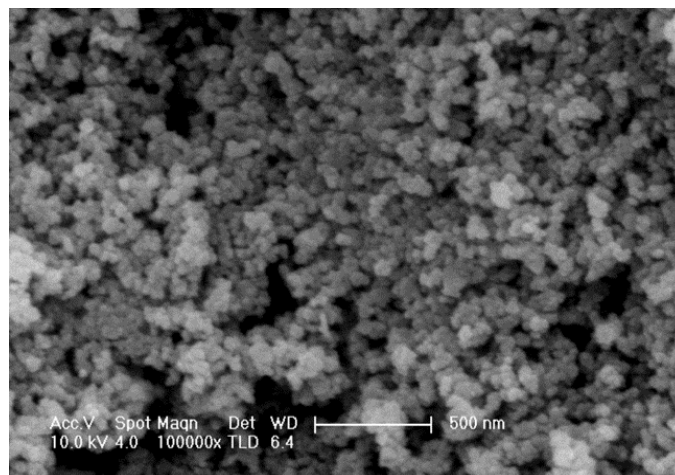


Fig. 3. SEM micrographs of TiO₂ nanoparticles

Due to the increasing demand in modern organic processes for reusability of catalysts, we decided to investigate the efficiency of this nanoparticles (TiO₂) as heterogeneous catalyst in the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles under solvent-free condition. Initially, the one-pot four-component coupling of benzil, benzaldehyde, aniline, and ammonium acetate as a simple model substrates was investigated to establish the feasibility of the strategy and optimize the reaction conditions.

A mixture of benzil (1mmol), benzaldehyde (1mmol), and aniline (1mmol) and ammonium acetate (1mmol) was heated on the oil bath at different temperatures in the presence of various amounts of nano-TiO₂ as

heterogeneous catalyst under solvent-free conditions (Table 1). As can be seen from this Table, the yield of compound **5a** is affected by the catalyst amount and reaction temperature. No product was obtained in the absence of the catalyst (Entry 1) or in the presence of the catalyst at room temperature (Entry 2) indicating that the catalyst and temperature are necessary for the reaction. Increasing the amount of the catalyst and reaction temperature up to 20 mol% and 110 °C, respectively, increased the yield of the product **5a**. Further increase in both catalyst amount and temperature did not increase the yield noticeably (Entries 10-18).

Table 1. Effect of nanoTiO₂ amount and temperature on the model reaction

Entry	Amount of catalyst (mol%)	T (°C)	Time(min)	Yield ^b (%)
1	None	110	60	None
2	15	r.t.	60	None
3	10	110	40	62
4	10	130	40	76
5	10	140	40	89
6	10	150	40	82
7	15	110	40	68
8	15	130	45	74
9	15	140	45	78
10	15	150	45	72
11	20	100	45	54
12	20	110	40	93
13	20	120	45	79
14	20	130	40	75
15	25	110	40	42
16	25	130	40	52
17	25	140	40	66
18	25	150	40	68

^a 1 mmol benzil, 1 mmol benzaldehyde, 1 mmol aniline, and 1 mmol ammonium acetate under neat conditions. ^b Isolated yields

Also, the model reaction was carried out in various solvents such as EtOH, H₂O, CHCl₃ and CH₂Cl₂ using 20 mol% of the catalyst. The use of H₂O gave the product **5a** in low yield (48 %). MeOH, CH₂Cl₂ and CHCl₃ gave moderate yields 60%, 60%, and 63% respectively. In addition the use of EtOH gave the product **5a** in good yield (84%). We next made a study on the catalytic activity of TiO₂ powdered loading in model reaction. In comparison with TiO₂ nanoparticles, the reaction times were longer and the yield were considerably lower. Under the above optimized conditions, the scope of this MCR process was next examined using various aromatic aldehydes and primary amines (Table 2).

In all cases, the obtained yields were excellent without formation of any side products such as 2, 4, 5-trisubstituted imidazoles. Aromatic aldehydes containing electron-donating or electron-withdrawing groups and various primary amines reacted efficiently and gave the expected products with excellent yields in relatively short reaction times. While aliphatic aldehydes such as pentanal and butanal produced only trace amounts of imidazoles that could not be isolated, aliphatic amines, such as methyl amine, produced high yield of the corresponding imidazole (Table 2, entry 13).

Table 2. Nano TiO₂ catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted^a

Entry	Ar	R	Product ^b	Time(min)	Yield ^c (%)	m. p. (°C)	
						Found	Reported
1	C ₆ H ₅	C ₆ H ₅	5a	40	93	215-218	213-215 ¹²
2	C ₆ H ₅	CH ₂ C ₆ H ₅	5b	30	92	162-164	161-163 ¹²
3	4-NO ₂ C ₆ H ₄	4-MeC ₆ H ₄	5c	45	80	221-222	220 ¹⁰
4	4-ClC ₆ H ₄	C ₆ H ₅	5d	45	85	149-150	146-148 ¹²
5	4-CH ₃ C ₆ H ₄	CH ₂ C ₆ H ₅	5e	45	75	165-166	167 ¹⁰
6	4-CH ₃ C ₆ H ₄	C ₆ H ₅	5f	30	91	180-183	183-184 ¹²
7	4-ClC ₆ H ₄	4-NO ₂ C ₆ H ₄	5g	60	79	168-169	---
8	4-NO ₂ C ₆ H ₄	CH ₂ C ₆ H ₅	5h	45	81	165-167	---
9	4-CH ₃ C ₆ H ₄	CH ₂ C ₆ H ₅	5i	45	87	160-162	163-165 ¹²
10	4-ClC ₆ H ₄	CH ₂ C ₆ H ₅	5j	30	82	163-165	163-164 ¹⁰
11	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	5k	60	92	155-159	--
12	4-CH ₃ OC ₆ H ₄	CH ₂ C ₆ H ₅	5l	60	93	158-160	155-157 ¹²
13	C ₆ H ₅	CH ₃	5m	45	80	142-144	144-145 ¹⁸

^a1 mmol benzil, 1 mmol aromatic aldehyde, 1 mmol primary amine, 1 mmol ammonium acetate and 0.20 mmol nano TiO₂ at 110 °C under solvent-free conditions. ^bThe products were characterized by comparison of their spectroscopic and physical data with authentic sample synthesized by reported procedures. ^c Isolated yields.

The principle advantage of the use of heterogeneous solid acid catalysts in organic transformations is their reusability. Hence, we decided to study the catalytic activity of recycled nano TiO₂ in the synthesis of compound **5a**. After the completion of the reaction, the catalyst was recovered according to the

procedure mentioned in experimental part and reused for a similar reaction. The catalyst could be reused at least seven times with only slight reduction in the catalytic activity (Table 3).

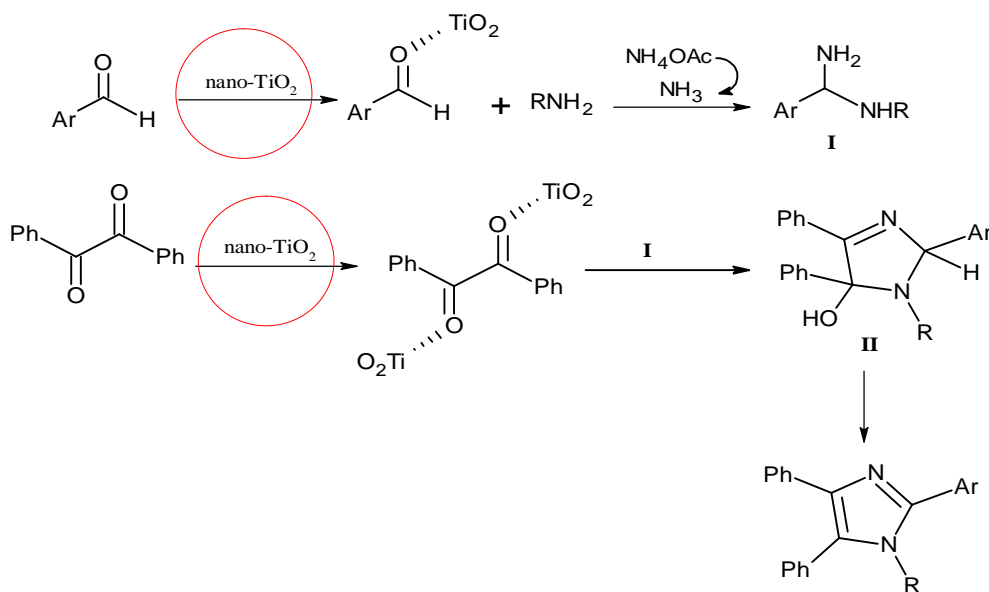
Table 3. Recovery and reuse of nano TiO₂ for the synthesis of **5a**

Cycle	Yield ^a /%
1	93
2	93
3	91
4	90
5	90
6	88
7	88
8	82
9	80
10	76

^aisolated yield

N-nucleophilic attack of the primary amine and ammonia, obtained from NH₄OAc, at activated carbonyl group in aryl aldehyde by nano TiO₂ yields the intermediate **I** which subsequently

reacts with activated benzil to form intermediate **II**. Dehydration of this intermediate produces the final products (Scheme 2).



Scheme 2: Proposed mechanism for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using TiO₂ as catalyst.

4. CONCLUSION

In conclusion, nano TiO₂ has shown to be an excellent catalyst for one pot four-component synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles under solvent-free conditions. Easy isolation and recycling of the catalyst, simple work up procedure, short reaction time and excellent yields are some advantages of this method. Henceforth, this methodology works well and is environmentally benign and may prove beneficial to both academia and industry for the socio-economic change.

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