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# Nanocrystalline Titanium(IV) Oxide as an Efficient Heterogeneous Catalyst for Tandem Michael and Nucleophilic 1,2-Addition to Enones

M. Lakshmi Kantam,[a,]* Soumi Laha,[a] Jagjit Yadav,[a] B. M. Choudary,[b] B. Sreedhar[a]

[a] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad-500007, India
Fax: (+91)-40-27160921, e-mail: mlakshmi@iict.res.in, lkmannepalli@yahoo.com
[b] Ogene Systems (I) Private Limited, Hyderabad, India

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**Abstract:** Nanocrystalline titanium(IV) oxide was found to be an efficient heterogeneous catalyst for the conjugate 1,4-addition of indoles with α,β-unsaturated ketones to afford β-indolyl ketones in excellent yields. The subsequent catalytic 1,2-addition of $Me_3SiCN$ to carbonyl compounds can be performed in one pot with moderate to good yields. Low sensitivity towards traces of moisture and high tolerance of different functional groups make nanocrystalline titanium(IV) oxide suitable for carrying out multistep synthetic sequences.

**Keywords:** cyanosilylation; indoles; nanocrystalline titanium(IV) oxide; recycling; tandem reactions; α,β-unsaturated ketones

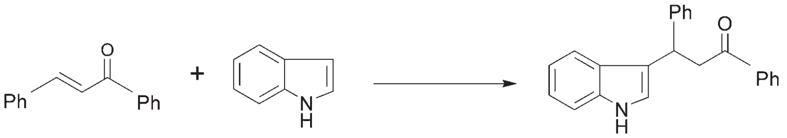
The accomplishment of successive reactions leading to the formation of several bonds by one-pot procedures provides useful methodologies for the synthesis of complex molecules.[1] The minimization of the number of steps not only provides more efficient synthesis but also allows the reduction of waste production.[2] In recent years, there has been increasing emphasis on the use and design of environment-friendly solid catalysts to reduce the amount of toxic waste. Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals and as catalysts for many organic transformations.[3,4] These high reactivities are due to high surface areas combined with unusually reactive morphologies.[5] Titanium dioxide is one of the most prominent materials for various kinds of industrial applications related to catalysis, e.g., the selective reduction of $NO_x$ in stationary sources, photocatalysis for pollutant elimination or organic synthesis, as well as uses in photovoltaic devices, sensors, and paints. Additional applications of importance include its use as a food additive, in cosmetics, and as a potential tool in cancer treatment.[6]

Michael addition of indoles to α,β-unsaturated ketones is an important C–C bond forming reaction as the resultant β-indolyl ketones are highly interesting building blocks for the synthesis of biologically active compounds and natural products.[7] They are usually carried out in the presence of catalytic or stoichiometric amounts of Lewis acids.[8] Recently, Marcantoni et al. used a $CeCl_3 \cdot 7\,H_2O$-NaI combination supported on silica gel for the Michael addition of indoles to α,β-unsaturated ketones.[9]

With the aim of evolving a Lewis acid-mediated Michael addition between an indole and an enone as a one-pot multistep transformation as discussed above, we designed and conceived the use of nanometal oxides composed of acidic sites, especially Lewis acidic sites. We herein report the conjugate 1,4-addition of indoles to α,β-unsaturated ketones to form β-indolyl ketones independently (Tables 1 and 2) as well as coupled with a subsequent nucleophilic 1,2-addition of TMSCN to the β-substituted ketone in a single pot (Table 3) using a catalytic amount of nanocrystalline titanium (IV) oxide (nano $TiO_2$). Both the reactions proceeded well with good to excellent yields.

When nano $TiO_2$ (10 mol %) was used to catalyze the Michael addition between an indole and an enone, the desired product was obtained in excellent yields (Table 1). No trace amount of the *N*-substituted product was observed. To optimize the reaction conditions, various parameters such as the effect of different nanomaterials and solvents were studied on the Michael addition reaction. The nano $TiO_2$ was found to be by far the more superior catalyst than other nano metal oxides such as CuO, ZnO and commercially available $TiO_2$. Among the solvents screened dichloromethane (DCM) gave the maximum yield. The catalytic activity of nano $TiO_2$ was evident when the reaction was conducted in the absence of the catalyst, no product was obtained even after 48 h.

**Table 1.** Screening of reaction parameters for the formation of 3-(3-indolyl)-1,3 diphenylpropan-2 one.[a]



| Entry | Solvent | Time [h] | Catalyst | Yield [%][b] |
|---|---|---|---|---|
| 1 | Acetonitrile | 24 | Nano $TiO_2$ | 22 |
| 2 | Ethanol | 24 | Nano $TiO_2$ | 28 |
| 3 | Methanol | 24 | Nano $TiO_2$ | 31 |
| 4 | THF | 24 | Nano $TiO_2$ | 50 |
| 5 | DCM | 6 | Nano $TiO_2$ | 75, 71[c] |
| 6 | Toluene | 6 | Nano $TiO_2$ | 52 |
| 7 | DCM | 36 | $TiO_2$ (commercial) | 0 |
| 8 | DCM | 18 | Nano ZnO | 42 |
| 9 | DCM | 18 | Nano CuO | 29 |

[a] *Reaction conditions:* indole (1.5 mmol), enone (1 mmol), catalyst (10 mol %), solvent (3 mL), room temperature.
[b] Isolated yields.
[c] Yield after fifth cycle.

The reaction of enone (**1a**) and indole (**2a**) (Table 2) in the presence of nano $TiO_2$ (10 mol %) and DCM (3 mL) at room temperature gave the 3-substituted indole in excellent yield in 6 h. To extend the scope of the reaction, indole and 2-methylindole were reacted with different α,β-unsaturated ketones. It is evident from Table 2 that the reaction proceeds well with different α,β-unsaturated ketones. The system works well with acyclic and cyclic substrates (Table 2, entries 1 and 6). No significant effect of substituted groups on the chalcone moiety was observed on the yield. (Table 2, entries 1, 3 and 4). The chemical yield increases when an electron-rich indole was used. (Table 2, entries 1 and 2). As can be seen from the Table 2, no external source of protons was required to increase the product yield in the case of a less electron-rich indole.[8a] The reaction does not require strict anhydrous conditions (Table 2, entry 1). Treatment of indole (**2a**) with methyl vinyl ketone in the presence of a catalytic amount of nano $TiO_2$ gave 1-(3′-indolyl)-butan-3-one in 92% yield. (Table 2, entry 10), No by-product, *N*-alkylated, dimeric or polymeric products was obtained.

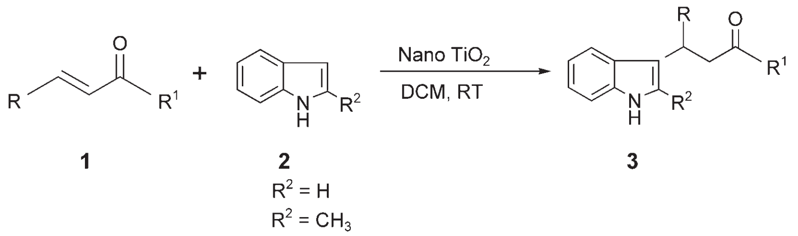
*One-pot 1,4–1,2-addition of indoles and TMSCN to α,β-unsaturated ketones:* Silylated cyanohydrins are highly versatile synthetic intermediates, which can be easily converted into a wide variety of important synthetic intermediates including α-hydroxy acids, α-amino acids, and β-amino alcohols.[10] There are a number of processes for the preparation of cyanohydrins from aldehydes and imines,[11] using trimethylsilyl cyanide (TMSCN) as the cyanating reagent, but the cyanation reaction of less reactive substituted and unsubstituted ketones has not been extensively exploited.[12] Recently Cozzi and Umani-Ronchi et al. used catalytic amounts of $InBr_3$ for the Michael 1,4-addition of indoles to α,β-unsaturated ketones and subsequent 1,2-addition of TMSCN to the enone.[8a]

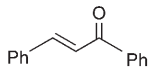
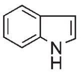
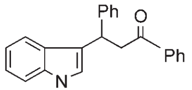
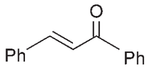
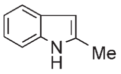
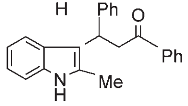
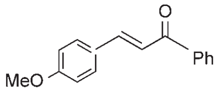
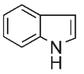
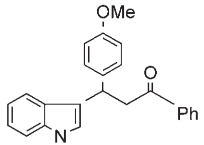
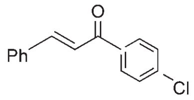
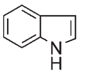
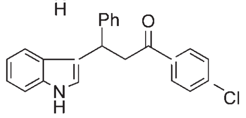
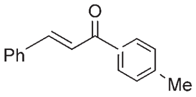
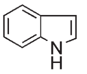
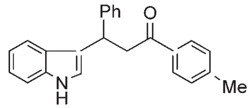
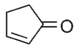
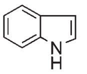
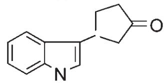
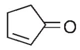
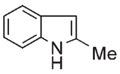
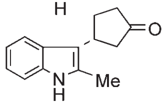
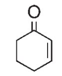
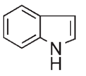
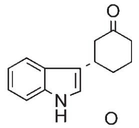
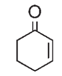
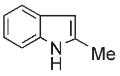
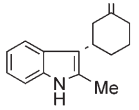
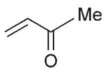
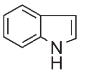
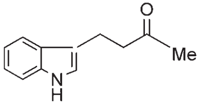
Herein, we have performed the 1,4-addition of α,β-unsaturated ketones with the appropriate nucleophiles, followed by nucleophilic 1,2-addition with TMSCN using nano $TiO_2$ in a single pot in good yields (Table 3). The 1,4-addition reaction was monitored by TLC. After complete conversion of the α,β-unsaturated ketone in about 10 h, TMSCN was added, which ultimately resulted in the formation of silylated cyanohydrins in good yields. A 1:1 mixture of diastereoisomers was obtained with unsubstituted indole (**2a**) (Table 3, entries 1, 2 and 4), and a moderate diastereoselection was obtained with the substituted indole (**2b**) (Table 3, entries 3 and 5).

The nanoparticles were characterized using several techniques, including XRD, TEM, TPD and BET. Both fresh and used catalysts were observed under TEM to understand the shape and size of the particles. As can be seen from Figure 1a – the fresh catalyst has particles well in the nano size range (10–20 nm) with well-defined shapes. Figure 1b shows the TEM image of the used catalyst after five recycles. Interestingly it is observed that the shape and size of the particles remain unchanged even after recycling. This supports that the morphology of the catalyst remains the same even after recycling.

The X-ray powder diffraction (XRD) patterns of the fresh and used nano $TiO_2$ do not differ in the range $2\theta = 0° - 80°$ which confirms the fact that the structure and morphology of the catalyst remain the same during the course of the reaction. The acidic site distributions are measured by ammonia TPD experiments, which were conducted on Auto Chem 2910 instrument. In a typical experiment for TPD studies, the samples were pretreated by passage of high purity (99.995%) helium

**Table 2.** Nano $TiO_2$-catalyzed Michael addition of α,β-unsaturated ketones with indole and 2-methylindole.[a]



| Entry | Enone | Indole | Product | Yield[b] [%] |
|---|---|---|---|---|
| 1 |  |  |  | 75, 71[c], 68[d] |
| 2 |  |  |  | 82 |
| 3 |  |  |  | 83 |
| 4 |  |  |  | 81 |
| 5 |  |  |  | 92 |
| 6 |  |  |  | 81 |
| 7 |  |  |  | 88 |
| 8 |  |  |  | 85 |
| 9 |  |  |  | 93 |
| 10 |  |  |  | 92[e] |

[a] *Reaction conditions:* all the reactions were carried out in anhydrous dichloromethane at room temperature, employing 10 mol % nano $TiO_2$, reaction time: 6 h.

[b] Isolated yields.

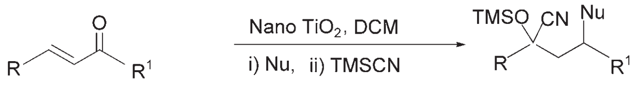
[c] Yields after fifth cycle.

[d] Reaction was done using bottle-grade DCM.

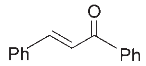
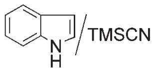
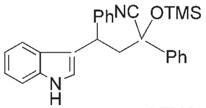
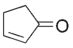
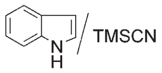
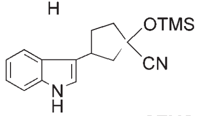
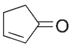
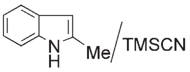
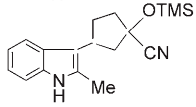
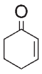
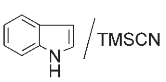
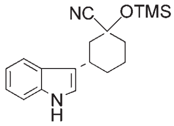
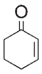
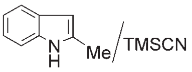
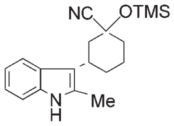
[e] Reaction time: 3 h.

(50 mL/min) at 473 K for 1 h. After pretreatment, the sample was saturated with pure anhydrous ammonia (75 mL/min) from a mixture of 10% $NH_3$-He at 353 K for 1 h and subsequently flushed with an He flow (50 mL/min) at 378 K for 2 h to remove physisorbed ammonia. TPD analysis was carried out from ambient tem-

**Table 3.** One-pot 1,4–1,2 addition of indoles to enones catalyzed by nano $TiO_2$.[a]



Nu = indole or 2-methylindole

| Entry | Enone | Nucleophiles | Product | Yield [%][b] | d.r[c,d] |
|---|---|---|---|---|---|
| 1 |  |  |  | 54, 50[e] | 50:50 |
| 2 |  |  |  | 61 | 50:50 |
| 3 |  |  |  | 65 | 65:35 |
| 4 |  |  |  | 68 | 50:50 |
| 5 |  |  |  | 73 | 71:29 |

[a] *Reaction conditions:* indole (1.5 mmol), enone (1 mmol), nano $TiO_2$ (10 mol %), TMSCN (9 mmol), anhydrous dichloromethane (3 mL), reaction time: 6 h, reaction done at room temperature.

[b] Isolated yields.

[c] d.r = diastereomeric ratio. The diastereomeric ratio was obtained from the $^1H$ NMR spectra of the compounds.

[d] Relative configuration was not assigned.

[e] Yields after fifth cycle.

perature to 1173 K at a heating rate of 10 K/min. In the ammonia TPD test, nano $TiO_2$ shows maximum desorption of ammonia over the commercial $TiO_2$, nano ZnO and nano CuO (Figure 2). Therefore the increased activity of nano $TiO_2$ over other samples tested is due to increased acidity. Besides this, nano $TiO_2$ with a higher surface area (500 $m^2/g$) and a higher porosity than commercial $TiO_2$ (SA: 10.69 $m^2/g$) contributes to the extraordinary chemical reactivity.

In conclusion, we have developed the nano $TiO_2$-catalyzed, simple and effective one-pot conjugate 1,4-addition of indoles to α,β-unsaturated ketones and subsequent nucleophilic 1,2-addition of TMSCN to the resulting β-substituted ketone which ultimately results in the formation of α-silyloxy-γ-indolyl nitriles in good yields. The efficiency of nano $TiO_2$ is well demonstrated and attributed to the enhanced acidic sites and surface area.

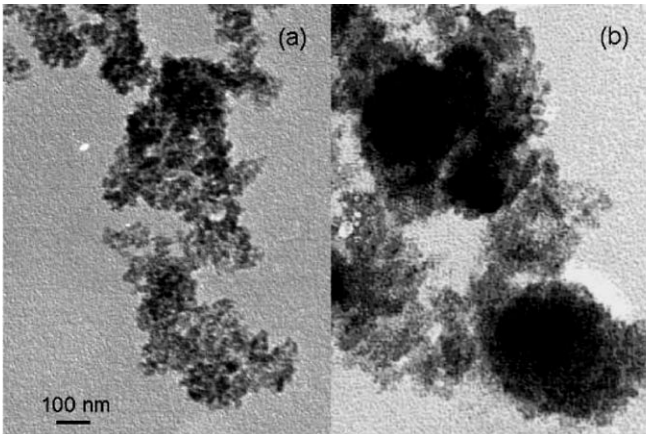


**Figure 1.** TEM images of the nano $TiO_2$ catalyst (a) before and (b) after use.

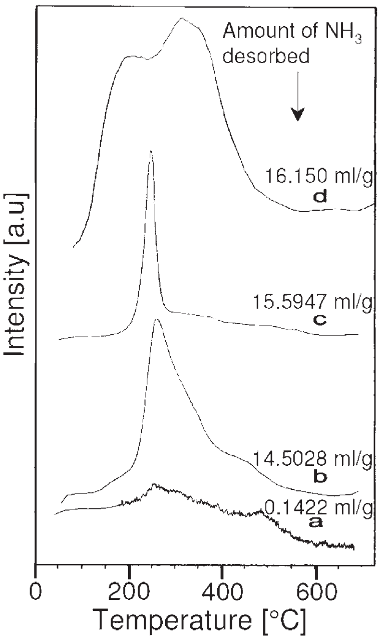


**Figure 2.** The ammonia TPD patterns of (a) commercial $TiO_2$, (b) nano CuO, (c) nano ZnO and (d) nano $TiO_2$.

## Experimental Section

### Typical Experimental Procedure for the Synthesis of 3-Alkylated Indoles

Nanocrystalline $TiO_2$ (10 mol %) was added to a mixture of indole (0.175 g, 1.5 mmol) and chalcone (0.208 g, 1 mmol) in anhydrous dichloromethane (3 mL) and stirred at room temperature for 6 h. After completion of the reaction (as monitored by TLC), the catalyst was centrifuged and washed with ether. The reaction was quenched by using a saturated solution of $NaHCO_3$ (3 mL) and the mixture extracted with ether. The combined organic layers were separated and dried over $Na_2SO_4$. The resultant organic layer was concentrated to give the crude 3-(3-indolyl)-1,3-diphenylpropan-2 one. Column chromatography was performed using silica gel (100–200 mesh) to afford pure 3-(3-indolyl)-1,3-diphenylpropan-2 one; yield: 75%. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta = 3.78$ (t, $J = 6.6$ Hz, 2H), 5.07 (t, $J = 7.2$ Hz, 1H), 6.96–7.58 (m, 13H), 7.91–7.96 (m, 3H).

### Typical Experimental Procedure for the Catalytic One-Pot Addition of Indole or 2-Methylindole and TMSCN to α,β-Unsaturated Ketones by NanoTiO$_2$

Nano $TiO_2$ (10 mol %) was added to 2-cyclopenten-1-one (0.082 g, 1 mmol) and 2-methylindole (0.198 g, 1.5 mmol) in anhydrous dichloromethane (3 mL) and stirred at room temperature until the disappearance of the starting cyclopentenone (checked by TLC). TMSCN (0.893 g, 9 mmol) was added by a syringe and the mixture was stirred at room temperature for 6 h. Finally the reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with ether. The organic phases were combined, dried over $Na_2SO_4$, and concentrated to afford the crude product. The crude product was purified by column chromatography on silica gel (100–200 mesh) to give pure 1-cyano-1-trimethylsilyloxy-3-(2-methyl-3-indolyl)-cyclopentane; yield: 65%; Diastereomeric mixture, d.r. = 65:35. $^1H$ NMR (200 MHz, $CDCl_3$) (major diastereoisomer): $\delta = 0.34$ (s, 9H), 2.06–2.61 (m, 6H), 2.39 (s, 3H), 3.49–3.59 (m, 1H), 7.08–7.14 (m, 2H), 7.27–7.29 (m, 1H), 7.58 (br, 1H), 7.70 (d, $J = 7.0$ Hz, 1H); (minor diastereoisomer): $\delta = 0.33$ (s, 9H), 3.61–3.78 (m, 1H).

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