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Graphical Abstract





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Visible-light-induced aerobic thiocyanation of indoles using reusable TiO_2/MoS_2 nanocomposite photocatalyst

Liang Wang,* Cancan Wang, Wenjie Liu, Qun Chen, and Mingyang He*

School of Petrochemical Engineering, Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou, 213164, P. R. China.

*Corresponding author. Tel.: +86-519-86330263; fax: +86-519-86330251. E-mail address: lwcczu@126.com; hemingyangjpu@yahoo.com

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ABSTRACT

 TiO_2/MOS_2 nanocomposite photocatalyst was prepared via simple one-step hydrothermal process. This nontoxic and inexpensive photocatalyst exhibited high activity towards the thiocyanation of indoles under visible light irradiation at room temperature. Simple work-up, good yields, as well as reusability of the catalyst are the major advantages of the present method.

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Recently, titanium dioxide (TiO₂) as an attractive heterogeneous photocatalyst has received much attention since it is very cheap, readily accessible, stable and nontoxic.^{1,2} More importantly, it benefits the photo-induced catalysis with heterogeneous features including stability and recyclability. Despite these impressive advantages of TiO₂ over conventional homogeneous photocatalysts, their utilization in organic transformations is still quite limited, especially under visible light irradiation.³⁻⁶ The limiting factors to the applications of TiO₂ as a photocatalyst lies in its wide band gap energy (~3.2 eV) and high recombination rate of photo-induced e⁷/h⁺ pairs at or near the catalyst surface.⁷⁻⁹ Much efforts have been made in recent years to narrow the band gap of TiO₂ and reduce the hole-electron pair recombination. Among them, modification of TiO₂ with other metal oxide nanoclusters such as NiO, FeO₈, CuO *etc.* have proven to be one of the most effective methods.^{3,10-13}

During the past decades, layered molybdenum disulfide (MoS_2) has been extensively investigated in photocatalysis due to its narrow band gap (1.3~1.8 eV), which provides not only visible-light-harvesting function but also high stability against photocorrosion.^{14,15} Moreover, high chemical stability as well as quantum confinement effects make it a suitable photosensitizer in heterogeneous semiconductor system. For instance, Zong et al¹⁶ reported the enhancement of photocatalytic H₂ production activity of CdS by loading MoS₂ as cocatalyst. Liu et al reported a one-step solvothermal synthesis of MoS₂/TiO₂ nanocomposites and excellent photocatalytic activity for H₂ evolution (119.5

 μ mol h⁻¹ g⁻¹) was observed with only 1 wt% loading of MoS₂.¹⁷ Xiang et al¹⁸ prepared a composite material consisting of TiO₂ nanocrystals grown in the presence of a layered MoS₂/graphene hybrid, which reached a high H₂ production rate (up to 165.3 μ mol h⁻¹ g⁻¹). Shen et al¹⁹ also disclosed an efficient MoS₂ nanosheet/TiO₂ nanowire hybrid nanostructure for visible light photocatalytic hydrogen evolution reaction. Just recently, Zhang et al²⁰ successfully applied a similar MoS₂/TiO₂ composite on the degradation of methyl orange. Acknowledged to the pioneer work that using modified semiconductor photocatalysts in hydrogen evolution area and photo-degradation of organic wastes, there is still much room to apply this appealing strategy to organic synthesis.

Thiocyano groups widely exist in natural products and pharmaceutical ingredients. They also serve as useful blocks to $1).^{21}$ construct sulfur-containing heterocycles (Figure Additionally, they are often considered as organic pseudohalides and can be easily converted to other functional groups. Electrophilic thiocyanation using thiocyanate salts in the presence of an oxidant is the major approach to deliver organic thiocyanates.²² However, a large excess amount of oxidants was usually required. Photocatalyzed thiocyanation reaction was also been reported, while these photocatalysts were expensive and could not be recovered and reused.²³ To our literature, thiocyanation reaction utilizing and cheap reusable semiconductor photocatalyst has not been reported yet. Herein, we disclosed the preparation of a TiO₂/MoS₂ nanocomposite

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photocatalyst and its application in the thiocyanation of indoles under visible light irradiation at room temperature.



Fig. 1Thiocyano group-containing natural products and bioactive compounds.

The TiO_2/MoS_2 nanocomposite was prepared by slightly modifying the reported literature¹⁷ via a simple hydrothermal process using cheap and readily available $TiCl_4$, sodium molybdate and thioacetamide as starting materials (see Supplementaty Material). The as-prepared TiO_2/MoS_2 nanocomposite was characterized by XRD, UV-vis and TEM.



Fig. 2 (a) XRD patterns of pure TiO_2 (red), pure MoS_2 (black) and TiO_2/MoS_2 (10: 1, molar ratio) nanocomposite (blue). (b) UV-vis spectra of pure TiO_2 (black), MoS_2 (red) and TiO_2/MoS_2 (10: 1, molar ratio) nanocomposite (blue). (c) TEM image of MoS_2 . (d) TEM image of TiO_2/MoS_2 (10: 1, molar ratio) nanocomposite.

Fig. 2 (a) presents the X-ray diffraction patterns for pure TiO₂, MoS₂ and TiO₂/MoS₂ (10: 1, molar ratio) nanocomposite. The characteristic diffraction peaks clearly indicate that the hybrid nanostructures with well-defined crystallinity consist of both MoS₂ and Anatase TiO₂. In the UV-vis study, TiO₂/MoS₂ nanocomposite exhibits intense absorption in both ultraviolet and visible-light regions (Fig. 2, b). The band gap energy (E_g) is estimated to be 2.99 eV based on the absorption spectrum and the (Ahv) = K(hv–Eg)ⁿ formula.²⁴ The TEM analyses show that the MoS₂ has a layered structure (Fig. 2, c), and TiO₂ nanoparticles (*ca.* 3~5 nm) disperse uniformly on the surface of the MoS₂ layer.

With the TiO₂/MoS₂ nanocomposite in hand, we start to explore its photocatalytic activity towards thiocyanation of indoles, and the results are summarized in Table 1. As shown from Table 1, no reaction occurred in the presence of either Anatase TiO₂ or Rutile TiO₂ under visible-light irradiation. A 42% yield of product **2a** was obtained by employing TiO₂/MoS₂ (100: 1, molar ratio of Ti to Mo) nanocomposite as the photocatalyst, indicating the hybridization structure have a synergistic effect in the present process. Further studies clearly showed that TiO₂/MoS₂ (10: 1, molar ratio of Ti to Mo) nanocomposite was the most suitable catalyst, providing **2a** in 93% yield (Table 1, entry 6). Only moderate yield was obtained in the presence of pure MoS₂ (Table 1, entry 8). Reactions in other solvents such as

DMF, DMSO, DCE, 1,4-dioxane, or CH₃OH led to decreased yields (Table 1, entries 9-13). A much lower yield was also obtained by decreasing the catalyst amount to 10 mg. Replacement of NH₄SCN with KSCN gave unsatisfactory yield (48%, Table 1, entry 15). Decreasing the amount of NH₄SCN to 2 equiv also led to a lower yield (73%, Table 1, entry 15). Finally, rather poor yield was observed under N₂ atmosphere, indicating O₂ is critical for this reaction (Table 1, entry 16).

Table 1 Optimized the reaction conditions.^a

	NH4SCN -	Catalyst solvent, 16 h rt, visible light	SCN
Entry	Catalyst	Solvent	Yield(%) ^b
1	TiO ₂ (Anatase)	CH ₃ CN	n.r.
2	TiO ₂ (Rutile)	CH ₃ CN	n.r.
3	TiO ₂ /MoS ₂ (100: 1)	CH ₃ CN	42
4	TiO ₂ /MoS ₂ (50: 1)	CH ₃ CN	55
5	TiO ₂ /MoS ₂ (20: 1)	CH ₃ CN	79
6	TiO ₂ /MoS ₂ (10: 1)	CH ₃ CN	93
7	TiO ₂ /MoS ₂ (5: 1)	CH ₃ CN	85
8	MoS_2	CH ₃ CN	63
9	TiO ₂ /MoS ₂ (10: 1)	DMF	48
10	TiO ₂ /MoS ₂ (10: 1)	DMSO	41
11	TiO ₂ /MoS ₂ (10: 1)	DCE	58
12	TiO ₂ /MoS ₂ (10: 1)	1,4-dioxane	53
13	TiO ₂ /MoS ₂ (10: 1)	MeOH	84
14	TiO ₂ /MoS ₂ (10: 1)	CH ₃ CN	$46^{\rm c}, 90^{\rm d}$
15	TiO ₂ /MoS ₂ (10: 1)	CH ₃ CN	48 ^e , 73 ^f
16	TiO ₂ /MoS ₂ (10: 1)	CH ₃ CN	11 ^g , 92 ^h

^aReaction conditions: **1a** (0.2 mmol), catalyst (20 mg, the ratio in parenthesis is the molar ratio of Ti to Mo), NH₄SCN (0.6 mmol, 3 equiv), solvent (2 mL), air, irradiation under a 14 W CFL at room temperature for 16 h. ^b Isolated yields. ^c 10 mg catalyst was used. ^d 40 mg catalyst was used. ^e 3 equiv of KSCN was used. ^f 2 equiv of NH₄SCN was used. ^g N₂ atmosphere. ^h O₂ atmosphere.

With these results in hand, we began to examine the scope and generality of the present method (Table 2).²⁵

Table 2. Reaction scope for indoles.^a



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^{*a*} Reaction conditions: **1** (0.2 mmol), TiO_2/MOS_2 (10: 1 molar ratio) (20 mg), NH₄SCN (0.6 mmol, 3 equiv), CH₃CN (2 mL), air, irradiation under a 14 W CFL at room temperature for 16 h, isolated yields. ^{*b*} Reaction for 36 h.

As illustrated in Table 2, a series of functional groups including chloro, bromo, methoxyl, methyl, as well as phenyl were well tolerated under the standard conditions. Substrates with electron-withdrawing groups, however, were inert towards the reaction even at a prolonged reaction time (2f, 48%; 2g, 27%; 2h, 12%; 2i, 21%, respectively). For *N*-methyl indole, the corresponding 3-thiocyano products were obtained in 94 and 84% yields respectively (2l and 2n), while *N*-Boc indole gave trace amount of the desired product (2o). It was worth noting that 3-methyl indole also reacted smoothly to deliver the 3-methyl-3-thiocyanatoindolin-2-one (2p) in 86% yield.

To demonstrate the utility of the present protocol, a scale-up reaction (10 mmol scale) was performed (Scheme 1). To our delight, this transformation afforded the desired product 2a in 83% yield (1.44 g) with a prolonged time (48 h).



Scheme 1 Gram-scale thiocyanation of 1a.

Another advantage of this developed protocol is the opportunity to recycle the nanocatalyst. Once the reaction is complete, in-flask extraction and centrifugal separation allows for isolation of the desired product, while the catalyst can be washed with ethanol and water. The recycled photocatalyst, as expected, showed good reusability in eight consecutive cycles with slight decrease in its activity (Fig. 3, a). Meanwhile, the recovered catalyst was examined by TEM and it was obvious that aggregation of TiO₂ was observed and the size of TiO₂ nanoparticles increased, which might accounted for the decreased activity after several runs (Fig. 3, b).



Fig. 3 Recycling experiment (a) and the TEM image of recovered TiO_2/MoS_2 (10: 1) nanocomposite after eight runs.

To gain insight into the mechanism, several control experiments were performed (Scheme 2). It was observed that the reaction was quenched when 3 equiv of radical scavenger, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), was added to the reaction mixture under standard conditions (Scheme 2, a). The reaction also did not take place in the absence of visible light, which strongly supports the radical mechanism (Scheme 2, b). Furthermore, the reaction was not quenched in the presence of 1 equiv of 1,4-Diazabicyclo[2.2.2]octane (DABCO), indicating that singlet oxygen is not involved in the reaction (Scheme 2, c).²⁶

On the basis of above experimental results, a plausible mechanism for this reaction was proposed (Scheme 3). Under visible-light irradiation, the CB of nanoscale MoS_2 is more positive than that of Anatase TiO_2 due to the quantum

confinement effects of nanoscale MoS_2 . The photogenerated electrons were then transferred into CB of anatase TiO_2 , thereby the photoinduced electrons and holes can be efficiently separated. The produced holes oxidized thiocyanate anion to thiocyanate radical, which attacked indole to generate radical intermediate **A**. Subsequently, intermediate **A** was oxidized to the intermediate **B**, which afforded the final product **2a** via deprotonation.



Scheme 3. Proposed mechanism.

In summary, we have developed a mild, inexpensive, and nontoxic visible-light-mediated photocatalytic system for thiocyanation of indoles by using TiO_2/MoS_2 nanocomposite. MoS_2 works as an efficient photosensitizer, and the hybridization structure exhibits a synergistic effect to enhance the photocatalytic activity under visible light irradiation. Good isolated yield and substrate compatibility, easy-to-hand workup process, and recyclability of the catalyst enable this protocol a more practical and environmentally benign alternative to known methods.

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- 25 **Typical procedure for the thiocyanation of indole and reuse of the catalyst:** To a solution of indole **1** (0.2 mmol)

and ammonium thiocyanate (0.6 mmol) in CH₃CN (2 mL) was added TiO₂/MoS₂ (10: 1, molar ratio, 20 mg). The reaction mixture was stirred under a 14 W CFL irradiation at room temperature for a certain time. After reaction (monitored by TLC), ethyl acetate was added, and the solid catalyst was recovered by centrifugation. The reaction mixture was extracted with ethyl acetate and washed with water. The combined organic phase was then dried over Na₂SO₄ and concentrated under reduced pressure to give the crude residue, which was purified by column chromatography with petroleum ether/ethyl acetate to afford the pure thiocyanated product **2**. The recovered catalyst was then washed with ethanol and deionized water, dried under vacuum, and reused for the next run.

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Highlights

- inexpensive Nontoxic and TiO_2/MoS_2 ► photocatalyst is prepared.
- Acception ►
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