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Visible-light mediated heterogeneous C–H functionalization: oxidative multi-component reactions using a recyclable titanium dioxide (TiO_2) catalyst†

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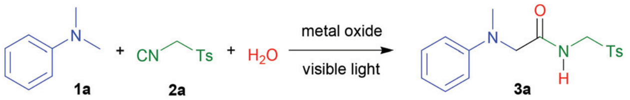
Visible-light mediated heterogeneous C–H functionalization of tertiary amines provides access to a variety of α-amino amides. An oxidative, titanium dioxide catalyzed, Ugi-type, three-component reaction has been developed in which the catalyst can be recycled without loss of activity.

Over the last few years titanium dioxide has been used as a viable photocatalyst and is attracting enormous interest due to its excellent chemical and photochemical stability, high availability, low cost and non-toxicity.[1] The application of TiO_2 in photocatalytic transformations is highly desirable for the development of environmentally acceptable processes. Moreover, the use of visible light to drive organic transformations provides a sustainable pathway for green synthesis and has received considerable interest in recent years.[2] Although TiO_2 has been widely used for the catalytic degradation of organic pollutants[3] and its application for the photocatalytic oxidation of alcohols to carbonyl compounds[4] and amines to imines[5] is well known, the number of examples of photocatalyzed C–C and C–heteroatom bond formations in organic synthesis is still limited.[6] Despite the significant advantages of heterogeneous inorganic photocatalysts over homogeneous catalysts, their use in the α-functionalization of tertiary amines remains less explored.

Therefore, we decided to investigate the α-functionalization of *N*,*N*-dimethylaniline and its derivatives using simple and inexpensive TiO_2 and visible light in the oxidative Ugi-type reaction (Scheme 1). The Ugi multi-component reaction[7] is a key reaction and has been intensively studied over the past few decades due to its efficacy in the synthesis of α-amino amides[8] which are highly important building blocks in organic synthesis. However, the application of heterogeneous photocatalysis in Ugi multi-component reactions is still unexplored, despite the inherent advantages of these reactions.[9–11]



Scheme 1 Photoredox multi-component reaction catalyzed by metal oxides.

Table 1 Optimization of reaction conditions[a]

Entry	Cat M_xO_y (*x* equiv.)	Solvent	Light source	Yield[b] (%)
1	TiO_2 (1)	CH_3CN	11 W lamp	33
2	TiO_2 (1)	Toluene	11 W lamp	15
3	TiO_2 (1)	CH_2Cl_2	11 W lamp	31
4	TiO_2 (1)	MeOH	11 W lamp	21
5	TiO_2 (1)	DMF	11 W lamp	34
6	TiO_2 (1)	Ether	11 W lamp	21
7	TiO_2 (1)	EtOAc	11 W lamp	47
8	TiO_2 (1)	THF	11 W lamp	57
9	ZnO (1)	THF	11 W lamp	27
10	TiO_2 (1)	Dioxane	11 W lamp	80
11	TiO_2 (0.5)	Dioxane	11 W lamp	71
12	TiO_2 (0.25)	Dioxane	11 W lamp	53
13	TiO_2 (1)	Dioxane	Blue LEDs	51
14	TiO_2 (1)	Dioxane	Green LEDs	47
15	TiO_2 (1)	Dioxane	In the dark	—
16	—	Dioxane	11 W lamp	—

[a] Reaction conditions: *N*,*N*-dimethylaniline **1a** (0.3 mmol), isocyanide **2a** (0.15 mmol), H_2O (10 equiv.), metal oxide M_xO_y, 1 mL solvent, 48 h, 30 °C. [b] Yield after chromatographic purification.

In order to develop a heterogeneous light mediated multi-component reaction, we began our investigations with the reaction of *N*,*N*-dimethylaniline (**1a**), *p*-toluenesulfonylmethyl isocyanide (**2a**) and H_2O in the presence of TiO_2 (Sigma-Aldrich P25). To our delight, we obtained the corresponding α-amino amide **3a** in 33% yield (Table 1, entry 1) when the reaction was carried out in acetonitrile. Although the yield of product **3a** was low, this result encouraged us to optimize the reaction conditions. Next, we studied the effect of solvent in this multi-component reaction. Interestingly, the best results were obtained when THF or dioxane was used as a solvent (Table 1, entries 8 and 10 respectively). Moreover, we examined

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ZnO as a photocatalyst. However, a significant decrease in the yield of the product **3a** was observed (Table 1, entry 9). We also examined the use of titanium dioxide in catalytic amounts (Table 1, entries 11 and 12) but we observed lower reactivity, indicating that the reaction is more efficient if one equivalent of metal oxide (amine–isocyanide–TiO_2 in a 2 : 1 : 1 ratio) is applied (Table 1, entry 10). Different light sources were assessed without any improvement on the yield of the α-amino amide (Table 1, entries 13 and 14). Furthermore, no product was observed when the reaction was performed without light or in the absence of a catalyst (Table 1, entries 15 and 16).

After the reaction conditions were optimized, we decided to study the substrate scope of the light-mediated, titanium dioxide catalyzed, multi-component reaction. In general, different amines **1** and different isocyanides **2** could be successfully applied providing the desired α-amino amides **3** in moderate to good yields (Table 2).

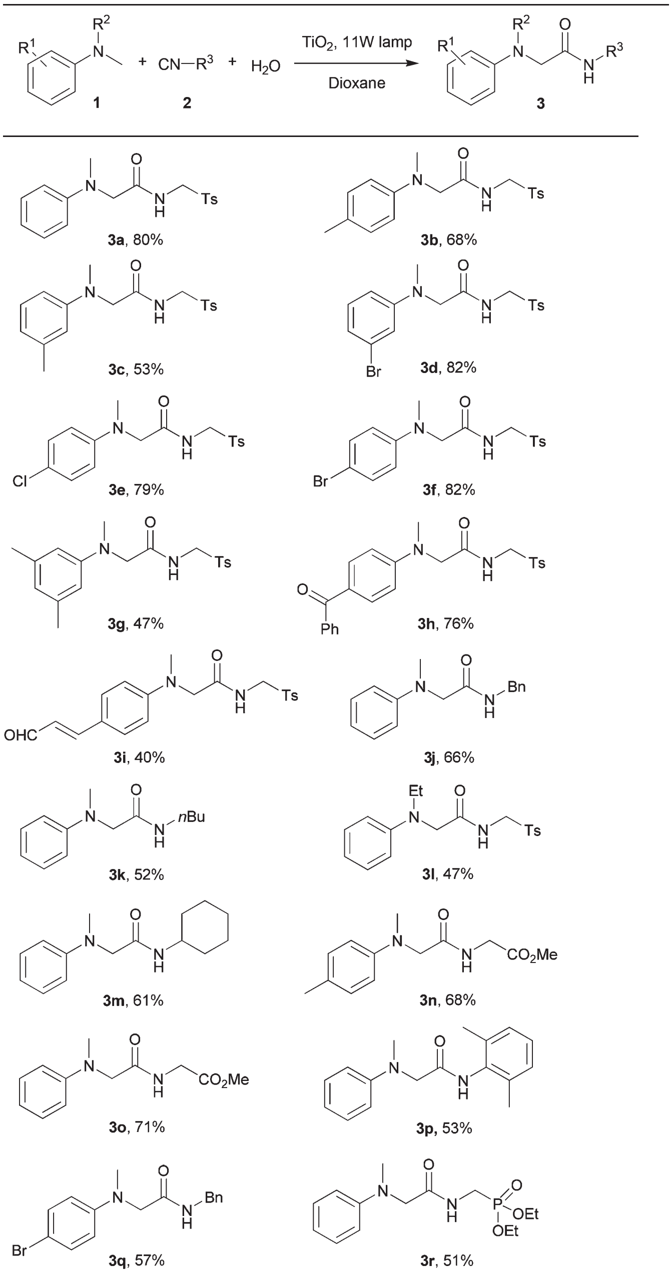
A variety of *N*,*N*-dimethylanilines, which contained a range of functionalities, were tested. Many valuable functional groups such as methyl, chloro, bromo, ketone and unsaturated aldehyde were tolerated under the reaction conditions, providing ample opportunity for further derivatization of the products. In addition to the dimethyl amines, *N*-ethyl-*N*-methylaniline was tested under optimized conditions, the corresponding α-amino amide **3l** being obtained with 47% yield. Moreover, different isocyanides reacted smoothly with *N*,*N*-dimethylaniline **1a** providing the corresponding products with moderate to good yields. The reaction is compatible with different isocyanides bearing functional groups such as esters or phosphonates. To summarize, this new protocol allows the convenient, technically easy and inexpensive synthesis of α-amino amides and circumvents the need for an expensive catalyst.

After studying the scope of the reaction, we decided to probe the recycling of the TiO_2 photocatalyst in order to demonstrate the advantage of having a cheap, readily available, heterogeneous and robust photocatalyst. Experimentally we only needed a simple centrifugal separation and the catalyst was reused without further treatment (Table 3). Gratifyingly, the TiO_2 photocatalyst could be efficiently recycled in 5 consecutive catalytic cycles without loss of selectivity and reactivity, underlining the efficiency of titanium dioxide as a photocatalyst for the Ugi multi-component type reaction.

The composition of a heterogeneous catalyst is quite important for its catalytic activity and often structural changes occur during the reactions. In order to obtain information about the catalyst structure, we examined samples of the TiO_2 before and after use in the photoredox Ugi multi-component reaction by means of high resolution transmission electron microscopy (HR-TEM). From these measurements no significant changes in the structure and shape of the catalyst were apparent (Fig. 1).[12] These measurements underline the robustness of the catalyst for the photocatalytic oxidative Ugi multi-component reaction.

A reaction pathway for this oxidative multi-component reaction, catalyzed by TiO_2 under visible light, is proposed in Scheme 2 and considers the amine–surface interaction which is believed to be responsible for the red shift in the absorption.[5] The first step of the cascade reaction is the light-induced oxidation of tertiary amine **1** into iminium ion (**A**) in the presence of a titanium dioxide catalyst. This is the key step of the reaction. Then, the nucleophilic attack of isocyanide **2** generates the nitrilium ion **B.** This nitrilium ion is trapped by water,

Table 2 Substrate scope of the visible light mediated multi-component reaction catalyzed by TiO_2 [a]



[a] Reactions were performed with amine **1** (0.3 mmol), isocyanide **2** (0.15 mmol), H_2O (10 equiv.) and TiO_2 (1 equiv.) in 1 mL of dioxane for 24–96 h at 30 °C. Yield of isolated products after column chromatography.

Table 3 Catalyst recycling in the visible-light mediated multi-component reaction[a]

Cycle	1	2	3	4	5
Yield of **3a** (%)	74	79	72	83	78

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.5 mmol), H_2O (10 equiv.), P25 TiO_2 (1. equiv.), 3 mL of dioxane, irradiation with a 11 W fluorescent lamp from 3 cm distance for 4 days, yields after column chromatography.

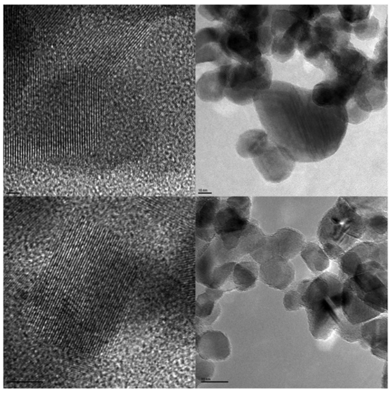
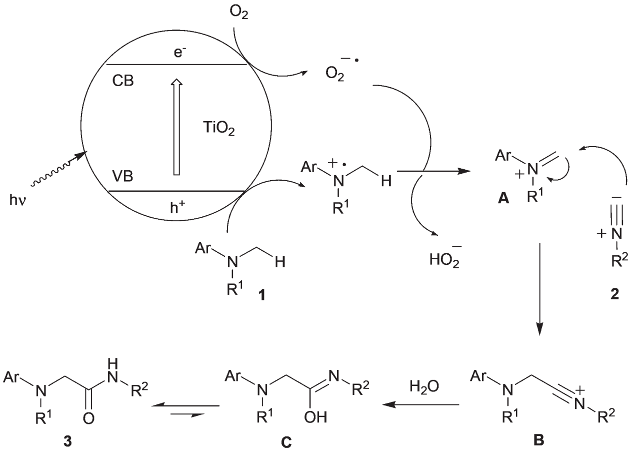


Fig. 1 HR-TEM and TEM analyses of TiO_2 before use (top) and after use (bottom).[12]



Scheme 2 Proposed reaction mechanism for the photoredox multi-component reaction catalyzed by TiO_2.

generating **C**. Finally, **C** tautomerizes to the corresponding amide, affording product **3**.

In summary, we have developed a new protocol for the synthesis of α-amino amides driven by visible-light catalysis and using cheap, robust, readily available and recyclable titanium dioxide. The advantage of using such a heterogeneous catalyst is the simplicity of its recycling and reuse. Thus, the protocol presented is both environmentally acceptable and economical. Further investigation into the applicability of this methodology for other multi-component reactions is currently ongoing and will be disclosed in due course.

Experimental

General procedure for the heterogeneous photocatalyzed Ugi type multi-component reaction

In a vial TiO_2 (P25) (12 mg, 0.15 mmol), amine **1** (0.3 mmol), isocyanide **2** (0.15 mmol) and H_2O (27 μL, 1.5 mmol) were dissolved in 1 mL of dioxane. The reaction mixture was stirred under irradiation with an 11 W fluorescent lamp (distance approx. 3 cm). After the reaction was complete the solvent was removed under reduced pressure and the crude mixture was directly charged on silica gel and purified by column chromatography (cyclohexane–EtOAc 8 : 2 to 6 : 4) to afford the corresponding α-amino amide **3**.

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