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Au-doped TiO_2 nanoparticles for selective photocatalytic synthesis of quinaldines from anilines in ethanol

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ABSTRACT

A convenient eco-friendly photocatalytic synthesis of quinaldines has been developed by a simple one-pot reaction of anilines in ethanol solution with Au-loaded TiO_2 under UV irradiation. Upon irradiation in the presence of Au-TiO_2, aniline and oxidation products derived from ethanol undergo condensation–cyclization to afford quinaldines.

Organic transformations for the synthesis of fine chemicals through semiconductor photocatalysis have become an important area of research for the last two decades.[1,2] The fact that some chemical reactions occur only in photocatalytic systems is particularly significant for this application.[3–6] However, in spite of several semiconductor-mediated reactions, examples of combined redox reactions are rather limited in the literature.[7–9] For multi-step synthesis, an illuminated semiconductor does offer a unique feature: an intermediate generated at one reactive site (oxidatively or reductively) can be the substrate at another reactive site. The integrated use of both the reactive sites can complete a sophisticated multi-step synthesis in 'one-pot'.

Quinoline and its derivatives have been the subject of much research due to their importance in various applications and their widespread biochemical significance. A large variety of quinoline derivatives have been used as antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, and tyrokinase PDGF-RTK inhibiting agents.[10–13] In view of these properties, great efforts have been made to develop new and efficient synthetic routes to quinoline derivatives in both synthetic organic and medicinal chemistry. Many of these routes have limitations, including long reaction time and harsh reaction conditions with hazardous reagents.

Apart from thermal synthetic routes to quinolines, very few studies on photocatalytic cyclization of nitrobenzene and its derivatives to yield the corresponding substituted quinolines and tetrahydroquinolines have been carried out. A number of photocatalysts such as TiO_2, TiO_2 with a co-catalyst (*p*-toluenesulfonic acid), and others have been used.[14–16] However, the selective formation of quinaldine derivatives from anilines has not been reported. From the point of view of selective conversion of fine chemicals, particular attention is devoted to the possibility of converting anilines to the corresponding quinaldines with good chemo- and regio-selectivity. Our laboratory has been engaged mainly with the development of modified semiconductor photocatalysts for environmental remediation and organic synthesis.[17–19] Thus in the present study, we examined photocatalytic conversion of aniline and its derivatives with absolute ethanol using TiO_2 or Au-TiO_2 as photocatalysts. To our knowledge this Letter describes the first synthesis of quinaldines from anilines under mild conditions using UV light. Nanometer-sized Au particles on TiO_2, (Au/TiO_2) were prepared by sol–gel method,[20] and characterized by AFM, TEM, X-ray diffraction (XRD), and diffuse reflectance spectroscopy (DRS) techniques (see Supplementary data, Figs. S1–S4).

The catalytic activity of Au-TiO_2 for the synthesis of quinaldine **2** was investigated for the reaction of aniline **1** with ethanol.[21] The concentrations of **1** and the product, quinaldine **2**, in EtOH solution upon photoirradiation (365 nm) were measured over times (Fig. 1). With pure TiO_2 (Fig. 1a), 6 h photoirradiation was required to achieve >99% consumption of **1**, affording **2** in only circa 50% and 2,3-dimethylindole (15%) in addition to small amounts of other reduction products (5%). The structure of each product was confirmed by GC/MS (see Supplementary data). The percentage yield was determined by comparison with the retention times of authentic samples and by co-injection with the authentic

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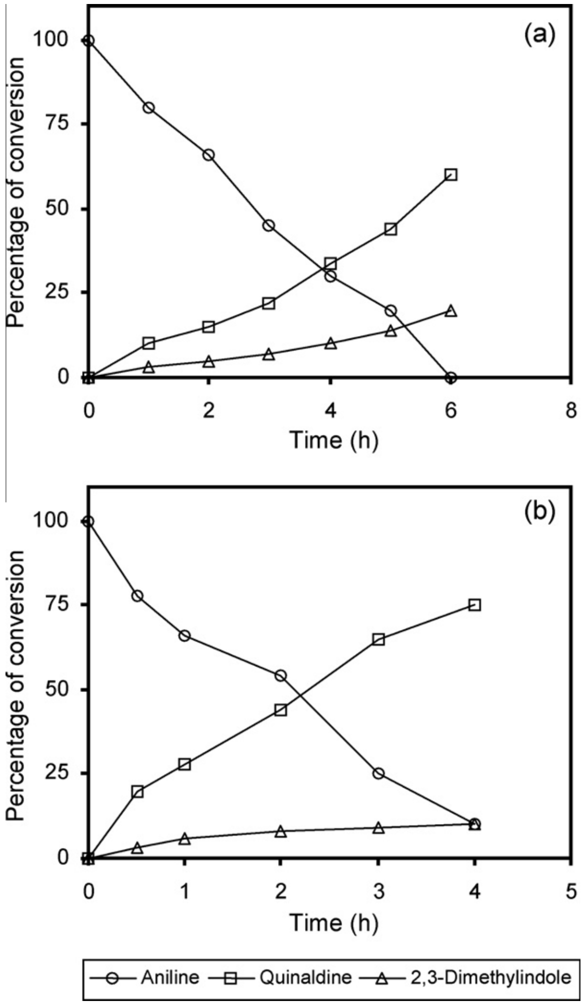


Figure 1. Time-dependent change in the concentrations of substrate and products during photoirradiation of aniline in neat EtOH with (a) TiO_2 and (b) Au-TiO_2 catalyst. Reaction conditions: 25 mM of aniline in ethanol, TiO_2 = 50 mg.

Table 2
Effect of water content on photocatalytic properties

Run	Conditions	Yield of quinaldine (%)	Conversion (%)
1	Neat ethanol	75	90
2	Ethanol–H_2O (99/1)	30	99
3	Ethanol–H_2O (98/2)	17	99
4	Ethanol–H_2O (96/4)	5	85

All reactions were performed with a 25 mM alcoholic solution of a reactant 50 mg of Au-TiO_2 suspension, $I = 1.381 \times 10^{-3}$ einstein L^{-1} s^{-1}, irradiation time = 4 h.

compounds. The main product identified was quinaldine. In contrast, Au (1%)-TiO_2 promoted the rapid and selective production of **2** by achieving 99% consumption of **1** with only 4 h irradiation to afford **2** in 75% yield and 2,3-dimethylindole (10%) (Fig. 1b). This indicates that Au-TiO_2 promotes rapid and selective quinaldine production.

The higher conversion of aniline with Au-TiO_2 (Fig. 1b) is due to the trapping of electrons by Au on the excited TiO_2. This enhances the charge separation between electron and hole.[22] This hole accelerates the oxidation of the alcohol to aldehyde, thus facilitating the rapid condensation between **1** and the aldehyde. The trapped electrons by the gold particles are consumed efficiently by the reduction of H^+ formed during the oxidation of the alcohol.[23] Controlled experiments demonstrated that aniline did not undergo any reaction in the absence of TiO_2 or without irradiation. The progress of the reaction was monitored by TLC and yields reported were estimated on the basis of GC. GC–MS chromatograms recorded at different reaction times of the photocatalytic conversion of aniline in ethanol are presented in Supplementary data (Fig. S5).

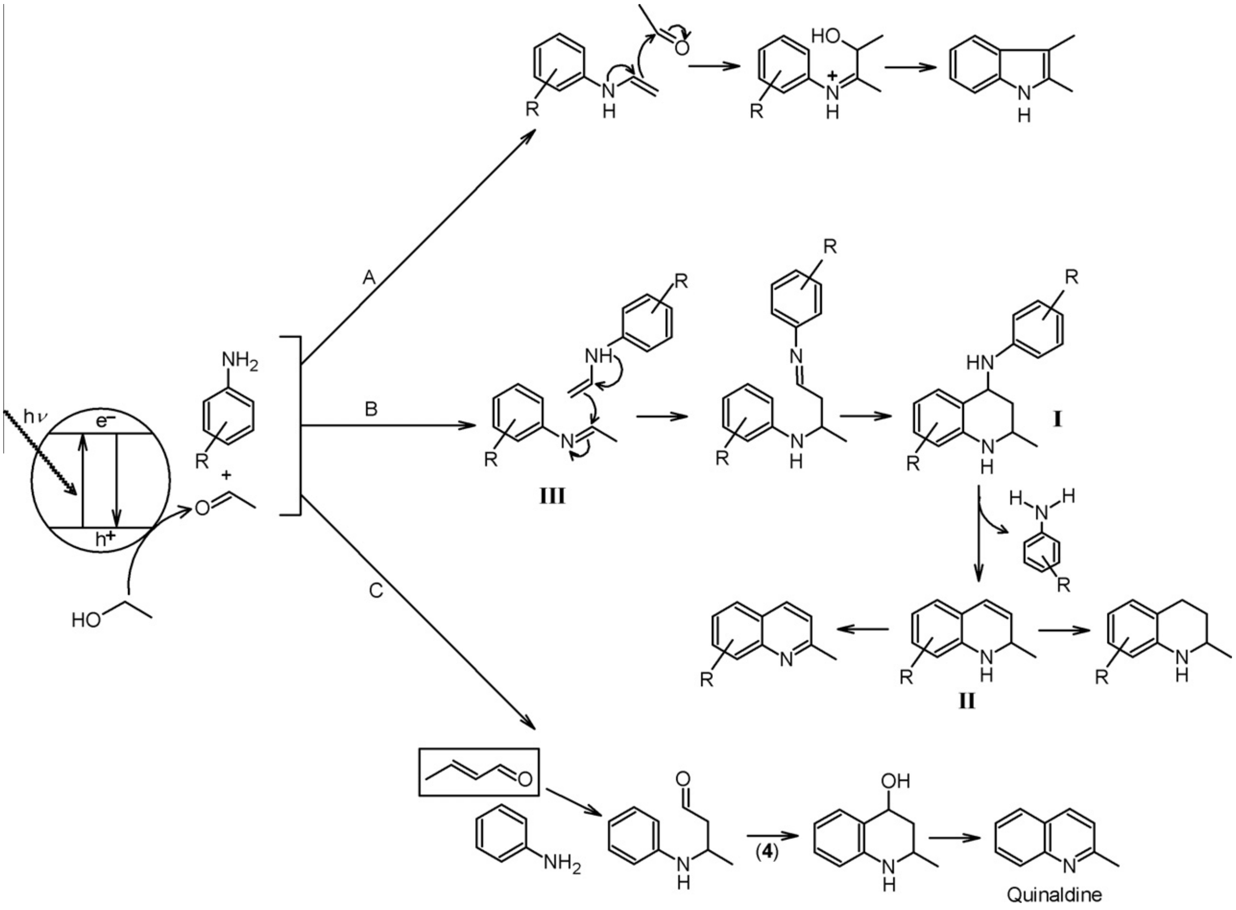
This process is tolerant for the synthesis of various substituted quinaldines. Photoirradiation of alcohol solutions that contained various anilines and the Au-TiO_2 catalyst successfully afforded the corresponding quinaldines (Table 1). In the case of *p*-toludine, the main product was 2,6-dimethylquinoline. *m*-Toludine and *o*-toludine produced 2,7-dimethylquinoline (80%) and 2,8-dimethylquinoline (68%), respectively. Irradiation of 3,5-dimethylaniline and 2,5-dimethylaniline led to the formation of 2,5,7-trimethylquinoline and 3,5,7-trimethylquinoline. When *p*-anisidine was used, 6-methoxyquinaldine was formed in slightly higher yield. In the case of 4-chloro- and 4-fluoroanilines, the yield of quinaldines was very low. This is attributable to photoinduced dehalogenation. Dehalogenated anilines have been identified in GC–MS analysis. It is interesting to observe that *p*-phenatidine has a conversion efficiency of 94% in the presence of irradiated Au-TiO_2. This is in contrast to the combined redox reaction of *m*-nitroanisole to tetrahydroquinoline, where the reaction proceeds rather slowly due to the presence of OCH_3 compared to those having alkyl substituent under the same reaction conditions.[14]

Table 1
Photocatalytic synthesis of various substituted quinaldines

Run	Conditions[a]	Products yield (%)	Byproduct (%)	Conversion
1	Aniline	Quinaldine (75) 2,3-Dimethylindole (10)	5	90
2	*o*-Toludine	2,8-Dimethylquinoline (68)	16	84
3	*m*-Toludine	2,7-Dimethylquinoline (80)	14	94
4	*p*-Toludine	2,6-Dimethylquinoline (70)	12	82
4	*o*-Anisidine	5-Methoxy-2-methylquinoline (78)	5	83
5	*m*-Anisidine	7-Methoxy-2-methylquinoline (84)	7	91
6	*p*-Anisidine	6-Methoxy-2-methylquinoline (80)	5	85
7	3,5-Dimethylaniline	2,5,7-Trimethylquinoline (76)	3	79
8	2,5-Dimethylaniline	3,5,7-Trimethylquinoline (77)	6	83
9	3,5-Dimethoxylaniline	5,7-Dimethoxy-2-methylquinoline (74)	7	81
10	*p*-Phenatidine	6-Ethoxyquinaldine (88)	6	94
11	*p*-Chloroaniline	6-Chloro-2-methylquinoline (14)	73	87
12	*p*-Fluoroaniline	6-Fluoro-2-methylquinoline (8)	76	84

All reactions were performed with a 25 mM alcoholic solution of a reactant, 50 mg of Au-TiO_2 suspension, $I = 1.381 \times 10^{-3}$ einstein L^{-1} s^{-1}, irradiation time = 4 h.

[a] Remaining unreacted amine.



Scheme 1. Schematic overview over the possible reaction pathways.

Other photocatalytic experiments have been carried out suspending Au-TiO_2 (50 mg) in different mixtures of EtOH–H_2O containing aniline (25 mM). Table 2 shows that the yield of quinaldine after 4 h irradiation decreases from 75% to about 10% with the increase in the amount of water. In water the photogenerated OH radicals can attack aniline in a non-selective manner. There is also the possibility that water favors the hydration of the accumulated aldehyde leading to the corresponding acid,[24] which can be further oxidized to CO_2 and H_2O. The decrease in yield may also be due to the reaction of imine intermediates with water.

Scheme 1 provides a tentative overview of plausible reaction mechanisms leading to the cyclization products identified by GC–MS. The initial step in the reaction which is necessary for all the reactions is the photocatalytic oxidation of the alcohol to aldehyde by valance band holes on Au-TiO_2. The photocatalytic formation of aldehyde from alcohol was well established.[25]

Pathways A and B (Scheme 1) suggest the formation of an imine (Schiff base) via the reaction between the aniline and acetaldehyde, whereas pathway C requires the intermediate formation of crotonaldehyde, the product of an aldol condensation of two acetaldehyde units. In fact, the condensation reaction to form imines is catalyzed in acidic conditions provided by the Au-TiO_2 surface. The acidic sites could be titanol groups, Ti···OH; generated during the oxidation of alcohols.[26] Note that crotonaldehyde was not detected by GC–MS under our experimental conditions. We believe that crotonaldehyde is produced in low concentration and consumed readily. In fact, when crotonaldehyde was made to react with *N*-ethylideneaniline thermally, the reaction was completed within 4 h.

More evidence for the reaction pathway B is the formation of tetrahydroquinoline, which was also detected by GC–MS (see Supplementary data). 2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl(phenyl)amine (**I**) can be formed via cycloaddition of the imine (**III**) to its enamine tautomer. Subsequent elimination of an aniline molecule yields the dihydroquinoline (**II**) as the intermediate. These results are in a good agreement with results published by Forrest et al. who demonstrated the viability of a mechanism for the thermal synthesis of 2-methylquinoline from aniline and acetaldehyde in the liquid phase that does not involve the formation of an α,β-unsaturated aldehyde.[27]

This new photochemical activity of Au-TiO_2 is of general interest in the field of photocatalysis. Further studies are in progress to establish the possible employment of solar active semiconductor catalysts for the exploitation of solar light and also to apply this reaction for heterocyclic amines with different alcohols.

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Supplementary data

Supplementary data (GC–MS chromatograms recorded at different reaction times of the photocatalytic conversion of aniline in ethanol and characterization of Au-TiO_2 by X-ray diffraction (XRD), atomic force microscopy (AFM), transmission electron microscope (TEM), and diffuse reflectance spectroscopy (DRS)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.071.

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20. Au(x)-TiO_2 samples, containing different gold loadings [x (wt %) = Au/(TiO_2 + Au)100; x = 0.05, 0.1, 0.2, 0.5, 1.0] were prepared by a conventional photodeposition method, in which photoirradiation of an aqueous solution home made TiO_2 with $HAuCl_4 \cdot 4H_2O$ afforded gray powder of the Au-TiO_2 catalyst.
21. In a typical experimental run, 50 mg Au-TiO_2 was suspended in 25 mL of an absolute ethanolic solution (Jiangsu Huaxi International Trade Co. Ltd, China) containing 25 mM of the aniline (Aldrich) and irradiated by a 365 nm medium-pressure mercury lamp (Sankyo Denki, Japan; intensity $I = 1.381 \times 10^{-6}$ einstein L^{-1} s^{-1}) after purging with N_2 for 30 min. N_2 bubbling (flow rate = 6.1 mL s^{-1}) and magnetic stirring of the suspension were continued throughout the reaction while the temperature was maintained at 30 ± 1 °C. Progress of the reaction was monitored by TLC. Product analysis was performed by GC analysis, Perkin–Elmer GC-9000 with a capillary column of DB-5 and flame ionization detector was used. GC/MS analysis was carried out using Varian 2000 Thermo with the following features: capillary column VF5MS (5% phenyl–95% methyl polysiloxane), 30 m length, 0.25 mm internal diameter, 0.25 μm film thickness, temperature of column range from 50 to 280 °C (10 °C/min), and injector temperature 250 °C, attached with mass spectrometer model SSQ 7000. The isolation was performed by column chromatography on a silica gel column by eluting with a co-solvent of hexane and ethyl acetate (volume ratio: 8:2).
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