A convenient method for the *N*-formylation of amines at room temperature using TiO₂-P25 or sulfated titania

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ABSTRACT

Semiconductor catalyzed *N*-formylation of a variety of amines using formic acid as formylating agent has been investigated. Primary and secondary amines were found to react efficiently with formic acid in the presence of TiO₂-P25 or sulfated titania giving *N*-formyl derivatives in high yields at room temperature. Sulfated titania is found to be more efficient and reusable than TiO₂-P25 for *N*-formylation of amines.

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1. Introduction

Metal-catalyzed reactions [1] are recognized as attractive and environmentally benign methods in synthetic chemistry with regard to the development of green chemistry. Solid catalysts with acidic/basic sites are considered as important functional materials in industrial processes. Nowadays notable progress has been made in the applications of semiconductor oxides as catalysts in organic synthesis [2,3]. Degussa TiO₂-P25 (80% anatase; 20% rutile) is a well known and widely investigated photocatalyst [4]. From a catalytic point of view, TiO₂ possesses a unique type of surface involving both redox and acid–base sites. In addition to high thermal stability, its amphoteric character makes titania a promising catalytic material. The textural and acid–base properties of titania depend greatly on method of preparation. Loading of sulfate using sulfuric acid makes TiO₂ more acidic as its surface is positively charged due to protonation (Scheme 1) [5]. Surface acidity was determined by the spectrophotometric method [6] on the basis of irreversible adsorption of organic base pyridine [7]. The amount of pyridine adsorbed by the 0.1 g of TiO₂-P25 and TiO₂-SO₄²⁻ are 40, 220 µg, respectively. Hence TiO₂-SO₄²⁻ can act as a strong Lewis acid.

Formylation of amines is a useful reaction in synthetic organic chemistry. Formamides are valuable intermediates in the construction of various pharmaceutically important compounds [8,9]. They are also useful reagents in Vilsmeier formylation reactions [10]. The formyl group is also an important amino protecting group in peptide synthesis [11]. In recent years, a number of methods have been reported on *N*-formylation of amines. Some of the formylation reagents are chloral [12], formic acid-DCC [13], formic acid-EDCI [14], formic acid esters [15], ZnCl₂ [16], KF-alumina [17], ammonium formate [18], CDMT (chlorodimethoxytriazine)[19], formic acid in sodium formate [20] and formic acid in polyethylene glycol [21]. Recently *N*-formylation of amines using sulfonic acid supported hydroxyapatite encapsulated γ-Fe₂O₃ was reported [22]. In this method there are difficulties in the preparation of catalyst and availability of reagents. Furthermore HCl evolution occurs during the preparation of catalyst. Most of the other *N*-formylation methods have disadvantages such as expensive reagents, formation of side products and thermal instability.

Our laboratory has been engaged mainly on the development of modified semiconductor photocatalysts for environmental remediation and organic synthesis [2,23–25]. Herein we report a recyclable, easily separable, eco-friendly and highly effective catalytic system TiO₂-P25 and TiO₂-SO₄²⁻ for the green synthesis of *N*-formyl derivatives at room temperature. TiO₂-SO₄²⁻, prepared by sol–gel method, was characterized by X-ray diffraction (XRD), FT-IR and scanning electron microscope (SEM) techniques [2]. Analysis of the SEM images of these catalysts reveals that the particles are uniformly distributed in spherical shape. Hence, SO₄²⁻ ion modification preferably retarded the aggregation. This facilitates the organic transformations. It is found from XRD analysis that the catalysts are in nanoparticulate form XRD peaks exactly matches with the anatase phase of TiO₂ and sulfate modification does not change

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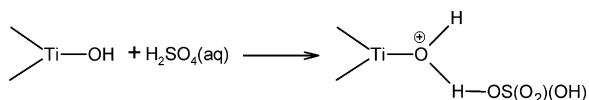
Scheme 1. Protonation of TiO_2 by aqueous H_2SO_4.

Scheme 2. Semiconductor catalyzed N-formylation of aniline with formic acid.

the phase. In general the surface area of the catalysts is the most important factor influencing the catalytic activity. The surface area of TiO_2-SO_4^{2-} was determined using the nitrogen gas adsorption method. The BET surface, pore volume and median pore width of TiO_2-SO_4^{2-} are given in Table 1. BET surface area of TiO_2-SO_4^{2-} ($142\,m^2\,g^{-1}$) is higher than the Degussa TiO_2-P25 ($50\,m^2\,g^{-1}$). The crystallite sizes of both prepared TiO_2 and TiO_2-SO_4^{2-} are 34.7 and 11.6 nm, respectively. The size of TiO_2-P25 is 30 nm [4]. Among the three catalysts TiO_2-SO_4^{2-} is having the minimum size. Both size reduction and retardation of aggregation result in increase in its surface area. This increases the photocatalytic activity of the catalyst in this reaction. Herein, we report the green synthesis of N-formylation of amines at room temperature using nano-TiO_2-SO_4^{2-}.

2. Experimental

2.1. Materials and methods

Aniline, 4-methylaniline, 4-methoxyaniline, 4-chloroaniline, 4-fluoroaniline, 4-carboxylaniline, 4-nitroaniline, piperazine, N-methyl aniline, cyclohexyl amine, n-butyl amine, monoethanol amine, 4-methylpiperazine, 1,2-phenylenediamine and formic acid (85%) (Aldrich chemicals) were used as received. A gift sample of TiO_2-P25 was obtained from Degussa (Germany). It is a 80:20 mixture of anatase and rutile. It has a particle size of 30 nm and BET specific area $50\,m^2\,g^{-1}$. Solvents of LR grade were distilled prior to use. AnalaR grade titanium isopropoxide (Himedia 98.0%), 2-propanol (Spectrochem 99.5%) and H_2SO_4 (Fischer 98%) were used as such.
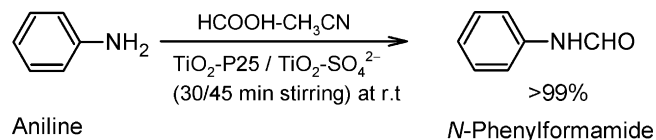
2.2. Apparatus

IR spectra were recorded using Avatar-330 FT-IR spectrophotometer using KBr pellets. For 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 GC model: Varian GC–MS-Saturn 2200 Thermo, capillary column VF5MS (5% phenyl-95% methylpolysiloxane), 30 m length, 0.25 mm internal diameter, 0.25 μm film thickness, temperature of column range from 50 to 280 °C ($10\,°C\,min^{-1}$), and injector temperature 250 °C. Proton and carbon NMR spectra were recorded on a BRUKER AVIII FT-NMR spectrometer operating at 500 MHz for all the samples. The specific surface areas of the samples were determined through nitrogen adsorption at 77 K on the basis of BET equation using a micrometrics ASAP 2020 V3.00 H.

2.3. Preparation of sulfate loaded TiO_2 photocatalysts

The catalyst with 5 wt% of SO_4^{2-} was prepared by sol–gel method, taking tetraisopropyl ortho-titanate (Himedia 98.0%) as

the starting material. 12.5 mL of tetraisopropyl ortho-titanate was dissolved in 100 mL of 2-propanol and to this solution 3.2 mL of 1 M H_2SO_4 was added drop wise under vigorous stirring. The resulting colloidal suspension was stirred for 4 h. The gel obtained was filtered, washed and dried in an air oven at 100 °C for 12 h. Addition of $BaCl_2$ to filtrate gave no precipitate indicating that all the sulfate ions were completely loaded on the gel. The sample was calcinated at 400 °C in a muffle furnace for 1 h. This catalyst contained 5 wt% of SO_4^{2-}. Similarly catalysts with 3 and 7 wt% of SO_4^{2-} were prepared with the same procedure. The bare TiO_2 was prepared with water instead of H_2SO_4.

2.4. General procedure for N-formylation of an amine

To a mixture of amine (1 mmol) and formic acid (3 mmol) in acetonitrile (8–10 mL), 0.1 g of TiO_2-SO_4^{2-} or TiO_2-P25 was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, ethylacetate was added to the solidified mixture and the insoluble catalyst was separated by filtration. The filtrate was dried over anhydrous Na_2SO_4. The solvent was evaporated and the product, obtained, was subjected to GC and GC–MS analysis for the determination of the yield of the products. The structure of products obtained had been confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and GC–MS analysis.

3. Results and discussion

No reaction was observed when a mixture of aniline (1 mmol) and formic acid (3 mmol) was stirred for 48 h in acetonitrile at room temperature. However, addition of a catalytic amount of TiO_2-P25/TiO_2-SO_4^{2-} to this mixture has rapidly induced N-formylation producing formanilide in high yields (Scheme 2). N-Formylation was carried out in the presence of TiO_2-P25, prepared TiO_2 (without sulfate) and sulfated titania with different concentrations of sulfate at room temperature in acetonitrile medium. The yield with TiO_2-P25 and prepared TiO_2 were 99.2 and 98.0%, respectively (for 45 min) (Table 2; entries 4 and 5). It was surprising to find that the reaction with sulfated titania could be completed in 30 min to give a quantitative yield of 99.2 (Table 2; entry 7). Structure of this product has been confirmed by spectral and GC–MS data [26]. The percentage yields of the product with 3 and 5 wt% of sulfate concentrations are 98.2 and 99.2, respectively (Table 2; entries 6 and 7). 5 wt% of sulfated titania was found to be the most efficient. When the sulfate

Table 1
Surface properties of TiO_2-SO_4^{2-}.

Properties	Values
BET surface area	142 ($m^2\,g^{-1}$)
Maximum pore volume	0.162300 cm^3/g
Median pore width	35.725 Å
Molecular cross-sectional area	0.1620 nm^2

Table 2
Effect of different catalysts (0.1 g) and solvent on N-formylation of amine (aniline) (1 mmol) at room temperature.

Entry	Catalyst	Solvent	Yield^a (%)
1	TiO_2-P25	Ethanol (45)	98.4
2	TiO_2-P25	$CHCl_3$ (45)	97.6
3	TiO_2-P25	DCM (45)	98.8
4	TiO_2-P25	CH_3CN (45)	99.2
5	Prepared TiO_2	CH_3CN (45)	98.0
6	3%-TiO_2-SO_4^{2-}	CH_3CN (30)	98.2
7	5%-TiO_2-SO_4^{2-}	CH_3CN (30)	99.2
8	7%-TiO_2-SO_4^{2-}	CH_3CN (30)	98.3

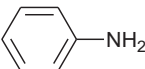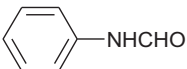^{a} Yields with respect to amine. Values within parentheses are indicating reaction time in minutes.
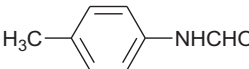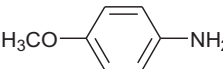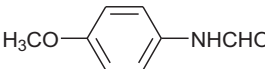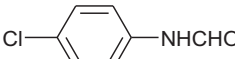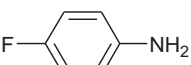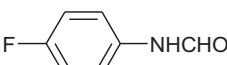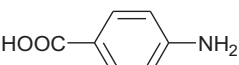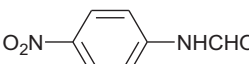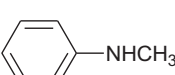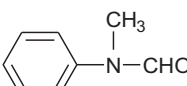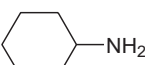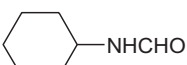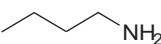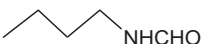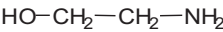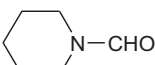
content was increased to 7 wt%, the product yield decreased slightly to 98.3% (Table 2; entry 8). Since the reaction was almost completed in 45 min, we compared the efficiencies of these catalysts by reducing the reaction time to 15 min. The yields with TiO_2-P25, prepared TiO_2, 3 wt% TiO_2, 5 wt% TiO_2 and 7 wt% TiO_2 were 85.0, 83.6, 90.2, 98.2 and 97.0%, respectively, at the time of 15 min. Hence, 5 wt% of sulfate was found to be the optimum level and this catalyst was used for N-formylation.

The N-formylation was carried out in the solvents acetonitrile, chloroform, dichloromethane and ethanol under the same reaction conditions using TiO_2-P25 as a catalyst. All the solvents gave a quantitative yield of product from 97.6 to 99.2% for 45 min (Table 2; entries 1–4). Because of high product yield acetonitrile was chosen as a solvent for further reactions. The effect of catalyst (TiO_2-P25) amount on the N-formylation was investigated by varying the catalyst amount from 0.05 to 0.15 g (Fig. 1). As the amount of the catalyst loading is increased from 0.05 to 0.1 g, the N-formylation increases from 88.1 to 99.2%. Above 0.1 g of the catalyst, no significant change in the conversion occurred. The optimum catalyst loading was found to be 0.1 g for N-formylation of 1 mmol of amine.

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protoc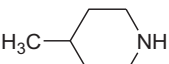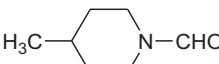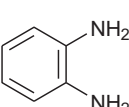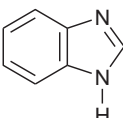ol, we used various substituted primary, secondary amines and compared the efficiency of catalyst TiO_2-P25 and sulfated titania for N-formylation reaction and the results obtained are summarized in Table 3. To the best of our knowledge this is the first report for the N-formylation reaction using semiconductor oxide as a heterogeneous catalyst at room temperature. All the reactions with substituted amines proceeded very cleanly at room temperature and no undesirable side-reactions

Table 3
Semiconductor catalyzed N-formylation of amines (1 mmol) with formic acid (3 mmol).

Entry	Substrate	Product	%Yield[a] with TiO_2-P25 (min)	%Yield[b] with TiO_2-SO_4^{2-} (min)
1	C6H5—NH2 (aniline)	C6H5—NHCHO	99.2 (45)	99.2 (30)
2	H3C—C6H4—NH2	H3C—C6H4—NHCHO	88.3 (300)	96.4 (240)
3	H3CO—C6H4—NH2	H3CO—C6H4—NHCHO	90.0 (300)	99.0 (240)
4	Cl—C6H4—NH2	Cl—C6H4—NHCHO	78.0 (420)	98.3 (360)
5	F—C6H4—NH2	F—C6H4—NHCHO	90.0 (420)	98.5 (360)
6	HOOC—C6H4—NH2	HOOC—C6H4—NHCHO	85.0 (480)	95.0 (420)
7	O2N—C6H4—NH2	O2N—C6H4—NHCHO	82.3 (480)	92.0 (420)
8	C6H5—NHCH3	C6H5—N(CH3)—CHO	Trace (980)	65.2 (920)
9	cyclohexyl—NH2	cyclohexyl—NHCHO	95.0 (60)	98.0 (45)
10	CH3CH2CH2CH2—NH2	CH3CH2CH2CH2—NHCHO	51.5 (180)	85.0 (120)
11	HO—CH2—CH2—NH2	HO—CH2—CH2—NHCHO	45.0 (180)	72.4 (120)
12	piperidine (NH)	N—CHO piperidine	Trace (780)	60.0 (720)
13	H3C—piperidine (NH)	H3C—piperidine N—CHO	Trace (960)	40.0 (900)
14	o-C6H4(NH2)2	benzimidazole	40.0 (180)	75.0 (120)

[a] Yields with respect to amine, catalyzed by TiO_2-P25.
[b] Yields with respect to amine, catalyzed by TiO_2-SO_4^{2-}.
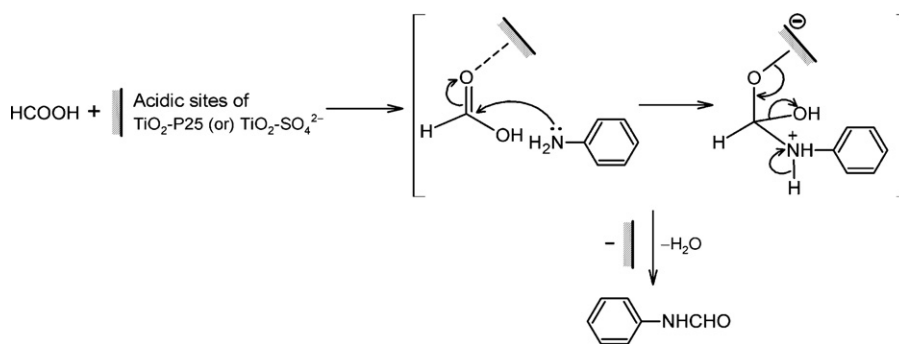
Scheme 3. Mechanism of TiO_2-P25 or TiO_2-SO_4^{2-} catalyzed *N*-formylation of aniline with formic acid.

were observed, although the yields were highly dependent on the substituents. Table 3 shows that electron-donating groups favored the formation of product (Table 3; entries 2 and 3). In contrast, electron-withdrawing groups such as chloro, fluoro, carboxylic and nitro (Table 3; entries 4–7) gave the slightly lower yield with longer reaction times. With Diphenylamine no *N*-formylation occurred in both catalysts whereas *N*-methyl aniline and piperidines gave moderate yield with TiO_2-SO_4^{2-} (Table 3; entries 8, 12, 13). Cyclohexylamine gave good yield with both catalysts (Table 3; entry 9) when compared to aliphatic and monoethanol amine (Table 3; entries 10 and 11). When *o*-phenylenediamine was used, instead of *N*-formylation, cyclization occurred to give benzimidazole as a product (Table 3; entry 14). In all the cases sulfated titania is more efficient when compared to TiO_2-P25.

Acid–base and redox properties are more important surface chemical properties of metal oxide catalysts. Since TiO_2-SO_4^{2-} is found to be more acidic by pyridine absorption method it is more efficient in *N*-formylation of amine than TiO_2-P25. Hence, this reaction follows the mechanism of acid-catalyzed condensation reactions as shown in Scheme 3. This mechanism of the *N*-formylation reaction involves the complexation of catalyst with the formic acid, nucleophilic attack of lone pair of electrons present in the amine to carbonyl carbon of formic acid. Then dehydration occurs to give an *N*-formyl product. A similar mechanism has been proposed for this reaction with the catalyst $ZnCl_2$ [16].

Table 4
Reusability of catalyst on *N*-formylation of amine (aniline) (1 mmol) at room temperature.

Run	1	2	3	4	5
Yield[a] (TiO_2-P25)	99.2	50.0	Trace	–	–
Yield[b] (TiO_2-SO_4^{2-})	99.2	99.2	99.2	98.5	98.3

[a] Yields with respect to amine, catalyzed by TiO_2-P25.
[b] Yields with respect to amine, catalyzed by TiO_2-SO_4^{2-}.

3.1. Catalyst reusability

The possibility of recycling of the catalyst was examined for the reaction of aniline with formic acid. When the reaction was complete, ethyl acetate was added to the solidified mixture and the insoluble catalyst was separated by filtration. The separated catalyst could be used five times without any treatment and, no appreciable loss in its catalytic activity was observed for TiO_2-SO_4^{2-} (Table 4). But TiO_2-P25 loses 50% efficiency in the first cycle and becomes inactive after second cycle. This reveals sulfated titania is not only more efficient than TiO_2-P25 but also reusable for the *N*-formylation reactions.

4. Conclusions

We have developed a novel and efficient method for *N*-formylation of an amine with formic acid using TiO_2-P25 or TiO_2-SO_4^{2-}. This paper describes first the observation of semiconductor (heterogeneous catalyst) catalyzed *N*-formylation of amines using formic acid and it offers a simple, economical, environment friendly method for *N*-formylation of amines at room temperature. Sulfated titania is more efficient and reusable than TiO_2-P25 for the *N*-formylation reactions at room temperature. We also believe this novel methodology will find wide application in organic synthesis.

Acknowledgements

Fig. 1. Effect of catalyst loading on *N*-formylation of aniline with formic acid. Catalyst = TiO_2-P25, aniline = 1 mmol, formic acid = 3 mmol, solvent = acetonitrile (8–10 mL), time = 45 min (stirring at room temperature).

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[26] *N*-Phenylformamide: mp 47–49 °C, IR (KBr) (cm^{-1}): 3320, 3058, 1660, 1571, 1338, 1204. ^{1}H NMR (500 MHz, CDCl$_3$) (δ, ppm): 8.30 (s, 1H, CHO), 9.17 (bs, 1H, NH), 7.10–7.58 (m, 5H, aryl protons). ^{13}C NMR (500 MHz, CDCl$_3$) (δ, ppm): 163.24 (NHCO), 159.94 (C–NH), 118.83–137.12 (aryl carbons). GC–MS (m/z): 121.0 (M$^+$).