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Short Communication

An expeditious and solvent free synthesis of azine derivatives using sulfated anatasetitania as a novel solid acid catalyst

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ABSTRACT

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1. Introduction

Azines, $R_1R_2C=N-N=CR_1R_2$ have attracted great attention in organic synthesis as they are good synthons for obtaining heterocyclic compounds such as pyrazoles, purines and pyrimidines [1-5]. These compounds constitute an important class of compounds with unexpected biological activities [5-7]. The ability of azines derived from 2pyridinecarbaldehyde as polydentate ligand to form very stable complexes with different cations is well known [8]. The usual method for the preparation of azines involves treatment of carbonyl compounds with hydrazine hydrate and acetic acid in ethanol [9,10]. A number of methods have been reported for the synthesis of azines under various conditions [11–15], but most of them require elevated temperatures and complex catalysts. Hence, there is a need to develop a simple, eco-friendly method under mild conditions for the preparation of azines. Now the research in organic synthesis is mainly focused on the use of environmental benign catalysts under solvent free conditions [16-18]. Recently, Safari and Ravandi reported the synthesis of azine derivatives with hydrazine sulfate and triethylamine under solvent free conditions [19].

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 H₂SO₄ makes the catalyst more acidic [20] when compared to bare TiO₂. Since the surface of TiO₂ is

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Solid acid catalyst sulfated anatase-titania ($TiO_2-SO_4^{2-}$) has been used for the synthesis of azine derivatives from benzophenone hydrazone and ketones/aldehydes by simple physical grinding. This sulfated titania gives an excellent yield with short reaction time and is an inexpensive, easily recyclable catalyst for this reaction. © 2011 Elsevier B.V. All rights reserved.

positively charged due to protonation as shown in Scheme 1, it becomes more acidic. Surface acidity was determined by the spectrophotometric method based on the irreversible adsorption of an organic base pyridine [21,22]. The amounts of pyridine adsorbed by 1 g of TiO₂ and TiO₂–SO₄²⁻ were 1600 and 2200 μ g, respectively. This reveals that TiO₂–SO₄²⁻ has more acidic sites when compared to bare TiO₂.

Since synthesis of azine derivatives are rare in literature, herein we report a recyclable, easily separable, eco-friendly and highly effective catalytic system $TiO_2-SO_4^{2-}$ for the synthesis of azine derivatives in excellent yield by simple physical grinding of reactants using a mortar and pestle at room temperature. To the best of our knowledge this is the first report of azine derivatives in this catalytic way.

2. Experimental

2.1. Materials and methods

Acetophenone, 4-methylacetophenone, 4-bromoacetophenone, 4chloroacetophenone, 4-fluoroacetophenone, benzophenone (s.d.fine), benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4bromobenzaldehyde, 4-flurobenzaldehyde, 4-chlorobenzaldehyde, 4nitrobenzaldehyde, furfuraldehyde and pyridine-2-aldehyde (Aldrich Chemicals) were used as received. AnalaR grade titanium isopropoxide (Himedia 98.0%), 2-propanol (Spectrochem 99.5%), hydrazine hydrate (s.d.fine) and H₂SO₄ (Fischer 98%) were used as such. Benzophenonehydrazone was prepared according to the literature procedure [23].

Preparation of TiO_2 - SO_4^{2-} by sol-gel method and its characterization by FT-IR, SEM, EDS, XRD and BET surface area measurements were reported earlier [24,25]. Analysis of the SEM images of this catalyst reveals that the particles are uniformly distributed in spherical

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Scheme 1. Protonation of sulfated titania.

shape. It is found from XRD analysis that the catalyst is in nanoparticulate form, and the sulfate modification does not change its anatase phase. The crystallite sizes of both prepared TiO_2 and $TiO_2-SO_4^{2-}$ are 34.7 and 11.6 nm, respectively. SO_4^{2-} ion modification retarded the aggregation. BET surface area of $TiO_2-SO_4^{2-}$ (142 (m² g⁻¹)) is higher than the prepared TiO_2 (86 m² g⁻¹). Size reduction increases its surface area, which enhances its catalytic activity in this reaction.

2.2. Apparatus

IR spectra were recorded using an Avatar-330 FT-IR spectrophotometer using KBr pellets. For GC analysis, a Perkin-Elmer GC-9000 with a capillary column of DB-5 and flame ionization detector was used. GC/MS analysis was carried out using a 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 μ m 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 400 MHz for all the samples.

2.3. Preparation of 1-(diphenylmethylidene)-2-(1-phenylethylidene) hydrazine, 3a – procedure

To a mixture of benzophenone hydrazone (1 mmol) and acetophenone (1 mmol) in dry media, 0.1 g of $TiO_2-SO_4^{2-}$ was added and the mixture was ground in a mortar with a pestle at room temperature

for 1 min. Completion of the reaction was tested by Thin Layer Chromatography (TLC). After completion of the reaction, ethanol was added to the solidified mixture and the insoluble catalyst was separated by filtration. The filtrate was dried over anhydrous Na₂SO₄. The solvent was evaporated to get the product. Then it was subjected to GC and GC–MS analysis for the determination of the product yield. The structure of product obtained was confirmed by FT-IR, ¹H NMR, ¹³C NMR and GC–MS analysis.

2.4. Preparation of bis(diphenylmethylidene)hydrazine, 30 - procedure

To a mixture of benzophenone hydrazone (1 mmol) and benzophenone (1 mmol) in dry media, 0.1 g of $TiO_2-SO_4^{2-}$ was added and the mixture was irradiated under microwave oven at 480 W for 8 min. Completion of the reaction was tested by TLC. After completion of the reaction, ethanol was added to the solidified mixture and the insoluble catalyst was separated by filtration. The filtrate was dried over anhydrous Na₂SO₄. The solvent was evaporated and the pure product was obtained. Then it was subjected to GC and GC–MS analysis for the determination of the yield of the products. The structure of product was confirmed by FT-IR, ¹H NMR, ¹³C NMR and GC-MS analysis. Spectral data of the some selected compounds are given below.

2.5. 1-(Diphenylmethylidene)-2-(1-phenylethylidene)hydrazine, 3a

m.p. = $105-107^{\circ}$ C; IR (KBr) (cm⁻¹) = 3053, 3024, 2926, 2838, 1595, 1563, 1441, 1361, 1295, 782, 694; ¹H NMR (CDCl₃, 400 MHz) (δ , ppm) = methyl proton 2.31 (s, 3H), other aromatic protons 7.11–7.62 (m, 15H), ¹³C NMR (CDCl₃, 100 MHz) (δ , ppm) = methyl carbon 15.6 and other aromatic carbons 126.7, 127.8, 128.2, 128.3, 128.3, 128.8, 128.9, 129.5, 129.6, 129.8, 135.5, 138.3, 138.4 and two C=N 158.8 and 159.6; GC–MS (m/z) = 299.2 (M + 1).



Scheme 2. The condensation reaction of benzophenone hydrazone 1a with acetophenone 2a, benzaldehyde 2f and benzophenone 2o catalyzed by sulfated titania.

Table 1

Synthesis of azine derivatives using sulfated titania under solvent free conditions.

| Entry | Hydrazone | Ketones/aldehydes | Azines | Grinding time (s) | Yield ^a (%) |
|-------|------------------------------|---|--|-------------------|------------------------|
| 1 | | ∠ C−CH ₃ 2a | N ^{-N} 3a | 60 | 98.0 |
| 2 | | Н ₃ С€-СН ₃ 2b | H ₃ C C C H ₃ C C H ₃ C C H ₃ C C H ₃ C C H ₃ | 60 | 96.0 |
| 3 | N ^{-NH2} L | | | 60 | 95.0 |
| 4 | | F-C-CH ₃ | F C C H N N N S C S d | 60 | 95.0 |
| 5 | N ^{-NH2} L | Br-C-CH ₃ | $ \begin{array}{c} Br \\ C \\ $ | 60 | 94.0 |
| 6 | N ^{-NH2} Ia | CHO 2f | | 45 | 98.0 |
| 7 | N ^{-NH2} C 1a | H ₃ C-CHO 2g | H ₃ C H ₃ C H ₃ C H ₁ C H N N N S H | 45 | 97.0 |

 Table 1 (continued)

| Entry | Hydrazone | Ketones/aldehydes | Azines | Grinding time (s) | Yield ^a (%) |
|-------|---|-----------------------------|---------------------------------------|-------------------|------------------------|
| 8 | N ^{NH2} C 1a | H ₃ CO-CHO 2h | H ₃ CO C N N N | 45 | 97.0 |
| 9 | N ^{NH2} C | CI-CHO 2i | | 45 | 97.0 |
| 10 | N ^{-NH₂} C 1a | F-CHO 2j | | 45 | 97.0 |
| 11 | N ^{-NH₂} C 1a | Br-CHO 2k | | 45 | 97.0 |
| 12 | N ^{NH2} L 1a | O ₂ N-CHO 2I | | 45 | 95.0 |
| 13 | N ^{-NH2} C | CHO 2m | 3 | 45 | 97.0 |
| 14 | N ^{NH2} L 1a | N CHO | | 45 | 97.0 |
| 15 | N ^{-NH₂} C 1a | | | MW/8 min | 98.0 |

^a Yield with respect to hydrazone (mol%).



Fig. 1. Effect of catalyst loading. Catalyst = sulfated titania, benzophenone hydrazone = 1 mmol, acetophenone = 1 mmol, time = 60 s (grinding at solvent free condition in room temperature).

2.6. 1-benzylidene-2-(diphenylmethylidene)hydrazine, 3f

m.p. = 97–98°C; IR (KBr) (cm⁻¹) = 3055, 3025,1610, 1569, 1444, 1317, 765, 692; ¹H NMR (CDCl₃, 400 MHz) (δ , ppm) = N=C – H proton 8.62 (s, 1H), other aromatic protons 7.22–7.82 (m, 15H), ¹³C NMR (CDCl₃, 100 MHz) (δ , ppm) = C – H carbon 96.18 and other aromatic and ipso carbons 128.1–159.2 and C=N 161.8, GC-MS (*m*/*z*) = 285.1 (M+1).

2.7. 1-(4-bromobenzylidene)-2-(diphenylmethylidene)hydrazine, 3k

m.p. = $103 - 105^{\circ}$ C; IR (KBr) (cm⁻¹) = 3053, 2978, 2919, 1602, 1560, 1483, 1442, 1320, 1297, 776, 524; ¹H NMR (CDCl₃, 400 MHz) (δ , ppm) = N=C-H proton 8.45 (s, 1H), other aromatic protons 7.27–7.69 (m, 15H), ¹³C NMR (CDCl₃, 100 MHz) (δ , ppm) = C-H carbon 96.18 and other aromatic and ipso carbons 125.1, 127.5, 128.1, 128.9, 129.2, 129.7, 130.2, 131.8, 133.5, 135.5, 138.1, 157.8 and C=N 166.2, GC-MS (*m*/*z*) = 364.1 (M + 1).

2.8. Bis(diphenylmethylidene)hydrazine, 30

m.p. = $163 - 165^{\circ}$ C; IR (KBr) (cm⁻¹) = 3079, 3054, 1638, 1564, 1487, 1442, 1318, 767, 659; ¹H NMR (CDCl₃, 300 MHz) (δ , ppm) = aromatic protons 7.28–7.53 (m, 20H); ¹³C NMR (CDCl₃, 300 MHz) (δ , ppm) = aromatic carbons 127.8, 128.0, 128.6, 128.7, 129.3, 129.6, 135.5, 138.2 and C=N 158.9; GC-MS (*m*/*z*) = 361.2 (M + 1).

3. Results and discussion

When a mixture of benzophenone hydrazone (1 mmol) and acetophenone (1 mmol) without catalyst was ground for 3 min no reaction occurred. However, grinding the mixture with 0.1 g of TiO₂–SO₄^{2–} initiated a condensation reaction producing 98 mol% 1-(diphenylmethylidene)-2-(1-phenylethylidene)hydrazine (3a) in 60 s (Scheme 2), (Table 1, entry 1). When bare TiO₂ and ZrO₂ were used in the same reaction only trace of product was obtained. Sulfated ZrO₂ was prepared from ZrO₂ by the procedure reported for sulfated TiO₂-P25 [26] and used for this reaction under the same conditions. Product yield was only 10 mol% with sulfated ZrO₂. This reveals that TiO₂–SO₄^{2–} is more efficient than sulfated ZrO₂.

The effect of catalyst $(TiO_2-SO_4^{2-})$ dosage on the formation of azine 3a was investigated by varying the catalyst amount from 0.05 to 0.2 g (Fig. 1). When the concentration of the catalyst is increased from 0.05 to 0.1 g, formation of azine increases from 95.0 to 98.0 mol%. This is due to increase in the number of catalyst particles. Above 0.1 g of the catalyst, no significant change in the percentage of product formation occurred. The optimum catalyst loading is found to be 0.1 g for the conversion of 1 mmol of benzophenone hydrazone.

In order to show the generality and scope of this new protocol, we used various substituted ketones and aldehydes for condensation with benzophenone hydrazone and the results obtained are summarized in Table 1. Condensation with all aldehydes and ketones (except benzophenone; Table 1, entry 15) proceeded very cleanly at room temperature and no undesirable side-reactions were observed. Yields were not much affected by the substituents present in the ketones and aldehyes (Table 1, entries 1–12). Furfuraldehye and pyridine-2aldehyde also gave good yield (Table 1, entries 13 and 14). Overall, al-dehydes react faster than ketones with benzophenone hydrazone.



Scheme 3. Proposed mechanism for the condensation reaction of benzophenone hydrazone with acetophenone catalyzed by sulfated titania.

Table 2

Reusability of catalyst on condensation of benzophenone hydrazone (1 mmol) and acetophenone (1 mmol) under grinding at room temperature.

| Run | 1 | 2 | 3 | 4 | 5 |
|---|------|------|------|------|------|
| Yield ^a (TiO ₂ -SO ₄ ²⁻) | 98.0 | 98.0 | 98.0 | 97.0 | 97.0 |

^a Yields with respect to benzophenone hydrazone (mol%).

However, in the case of benzophenone, no reaction was observed when it was ground with benzophenone hydrazone at room temperature for 10 min in the presence of $TiO_2-SO_4^{2-}$. No product was obtained even by refluxing the mixture in alcohol (Scheme 2). This may be due to steric effect of two phenyl groups present in the benzophenone. This steric effect is also reflected with benzaldehyde and acetophenone. Benzaldehyde reacts faster than acetophenone with benzophenone hydrazone. Hence, synthesis of benzophenone azine was carried out under microwave irradiation. The use of microwaves in organic synthesis has attracted considerable attention in recent years due to short reaction time and improved product yield [27–29].

When a mixture of benzophenone hydrazone (1 mmol) and benzophenone (1 mmol) without solvent was irradiated in microwave oven (480 W) for 10 min, no reaction was observed. But addition of a 0.1 g of TiO_2 - SO_4^{2-} to this mixture initiated condensation reaction producing 98 mol% 1,2-bis(diphenylmethylene)hydrazine in 8 min under microwave irradiation (Scheme 2) (Table 1, entry 15).

Since the sulfated titania has more acidic sites, acid catalyzed mechanism is proposed for this reaction (Scheme 3). This mechanism involves the protonation of hydrazone with acidic $TiO_2-SO_4^{2-}$. This protonated hydrazone **1** condenses with acetophenone forming an intermediate **2** which on dehydration and deprotonation produces the product azine **3**. Solid acid catalyst $TiO_2-SO_4^{2-}$ promotes dehydration and deprotonation. The possibility of recycling the catalyst was examined for the reaction of benzophenone hydrazone with acetophenone. When the reaction was complete, ethanol 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 up to fifth run (97.0 mol%) (Table 2, entry 5).

4. Conclusions

In conclusion, sulfated titania is introduced as an excellent catalytic system for the synthesis of azine derivatives by simple grinding at room temperature. This catalyst is more efficient than sulfated ZrO₂ and bare TiO₂. This novel and practical method has the advantages of mild conditions, excellent yield of products and very short reaction

time. Another attractive feature of this green process is the reusability of solid acid catalyst, sulfated titania.

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