 Bull. Chem. Soc. Jpn. Vol. 84, No. 11, 1261–1266 (2011)

A Recyclable Solid Acid Catalyst Sulfated Titania for Easy Synthesis of Quinoxaline and Dipyridophenazine Derivatives under Microwave Irradiation

Balu Krishnakumar and Meenakshisundaram Swaminathan*

Department of Chemistry, Annamalai University, Annamalainagar 608 002, India

Received May 24, 2011; E-mail: chemres50@gmail.com

TiO_2–SO_4^{2-}, prepared by sol–gel method has been used for the synthesis of quinoxaline and dipyridophenizine derivatives under microwave irradiation. High-resolution transmission electron microscope (HR-TEM) and atomic force microscope (AFM) images reveal the corrosion of TiO_2 particles by sulfuric acid, which causes an increase in the acidity of the catalyst. Sulfate loading by H_2SO_4 increases catalytic activity of TiO_2. This catalyst gives an excellent yield with less reaction time and is an inexpensive, easily recyclable and efficient catalyst for this reaction.

Green chemistry is a rapidly developing new field since it provides a proactive avenue for the sustainable development of future science and technologies.[1] Green chemical synthesis uses highly efficient and environmentally benign synthetic protocols to deliver life saving medicines, accelerating lead optimization processes in drug discovery. For green synthesis it is desirable to avoid any organic solvents as a reaction medium and to use green catalysts.

Quinoxaline and its derivatives are an important class of benzoheterocycles[2] displaying a broad spectrum of biological activities[3,4] which has made them privileged structures in combinatorial drug discovery libraries.[5] Dipyridophenazines have been used as a metal ligand for the formation of ligand complexes with attractive features.[6] A number of synthetic strategies have been developed for the preparation of substituted quinoxalines and dipyridophenazines.[6–9]

Though a number of catalysts such as $Ga(OTf)_3$,[10] montmorillonite K-10,[11] sulfamic acid,[12] $CuSO_4 \cdot 5H_2O$,[13] Zn(L-proline),[14] I_2,[15,16] Ni nanoparticles,[17] cellulose sulfuric acid (CSA),[18] silica sulfuric acid (SSA),[19] Zn^{2+}–K-10 clay,[20] acidic alumina,[21] and MeOH/AcOH under microwave irradiation[22] have been used for this condensation reaction, they have a few constraints like the use of strong acids and high reaction temperatures. As the aforesaid methods are not compatible with heat or acid sensitive substrates, there is a need to develop an effective synthesis of quinoxalines employing more eco-friendly catalysts. Hence, recent research has been focused on finding new methods to improve the yield of this condensation reaction. Characterization of TiO_2–SO_4^{2-} by FT-IR, SEM, EDS, XRD, and BET surface area measurements were reported earlier.[23,24] The SEM image of TiO_2–SO_4^{2-} shows that the particles are uniformly distributed in spherical shape. SO_4^{2-} modification retarded the aggregation. XRD peaks exactly match with the anatase phase of TiO_2, and sulfate modification does not change the phase. TiO_2–SO_4^{2-} has similar 2θ values to TiO_2 but the peak intensities differ. The FWHM of TiO_2–SO_4^{2-} peaks are higher than TiO_2 and this broadening of peaks implies the decrease in crystalline size of TiO_2. Both size reduction and retardation of aggregation result in increase in surface area of the catalyst. Morphology of TiO_2–SO_4^{2-} has been further analyzed by high-resolution transmission electron microscope (HR-TEM) and atomic force microscope (AFM).

The use of microwaves in organic synthesis has attracted considerable attention in recent years, as this method shortens the time, enhances reaction rates, and improves product yields.[25–27] So, we tried the synthesis of quinoxaline and dipyridopyridine derivatives under irradiation with microwaves. Recently, we reported the condensation reaction of *o*-phenylenediamine (**1a**) and benzil (**2a**) in the presence of sulfated TiO_2 with different concentrations of sulfate at room temperature for 5 min in ethanol medium.[23,28] It was found that this reaction with 5 wt % sulfated TiO_2 could be completed in 5 min to give 99% yield of quinoxaline. Interestingly we found that this reaction when performed with the same catalyst under microwave irradiation in dry media (Scheme 1) could be completed in 1 min giving a yield of 99% of quinoxaline.

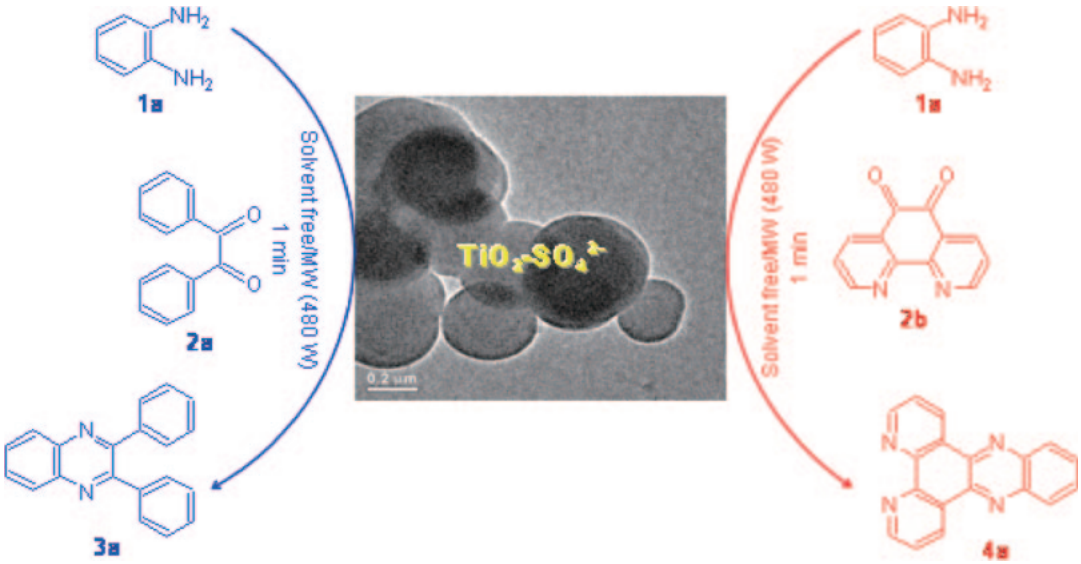
Some of the solid super acid catalysts prepared using sulfuric acid and metal oxides were reported for the alkylation reactions.[29,30] Herein we report a recyclable, easily separable, eco-friendly, and effective solid acid catalyst sulfated TiO_2 for the solvent free synthesis of quinoxaline and dipyridophenazine derivatives under microwave irradiation.

Aqueous sulfuric acid used in the preparation of the catalyst protonates titania hydroxyls by an acid–base reaction and hence the catalyst acts as a strong Lewis acid (Scheme 2).[31,32] Surface acidity was determined spectrophotometrically on the basis of irreversible adsorption of an organic base pyridine. The amount of pyridine adsorbed by 1 g of TiO_2 and TiO_2–SO_4^{2-} are 1600 and 2200 μg, respectively. This reveals that TiO_2–SO_4^{2-} has more acidic sites than TiO_2.[23]

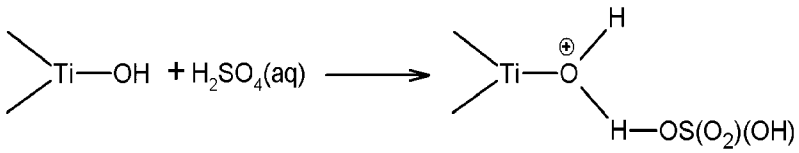
Experimental

Materials. *o*-Phenylenediamine, substituted diamines, and benzil (Aldrich). AnalaR grade titanium tetraisopropoxide

Published on the web November 9, 2011; doi:10.1246/bcsj.20110152



Scheme 1. The condensation reaction of *o*-phenylenediamine (**1a**) with diketone (benzil (**2a**) and 1,10-phenanthroline-5,6-dione (**2b**)) catalyzed by TiO_2–SO_4^{2-} under microwave irradiation.



Scheme 2. Protonation of titania hydroxys by sulfuric acid.

(Himedia 98.0%), 2-propanol (Spectrochem 99.5%), and H_2SO_4 (Fischer 98%) were used as such. 1,10-Phenanthroline-5,6-dione was prepared according to a literature procedure.[6]

Apparatus. An Avatar-330 FT-IR spectrophotometer was used for recording IR spectra. HR-TEM images were recorded using a JEOL JEML-3010 high-resolution transmission electron microscope. The working voltage of TEM was 300 keV. Proton and carbon NMR spectra were recorded on a BRUKER AVIII FT-NMR spectrometer operating at 500 MHz for all the samples. For GC analysis, a Perkin-Elmer GC-9000 with a DB-5 capillary column and flame ionization detector was used. GC/MS analysis was carried out using a Varian GC-MS-Saturn 2200 Thermo, capillary column VF5MS (5% phenyl–95% methyl polysiloxane), 30 m length, 0.25 mm internal diameter, 0.25 µm film thickness, column temperature from 50 to 280 °C (10 °C min^{-1}), and injector temperature 250 °C. Microwave LG ECN: MG-395 WA/01, MOD: MG-395 WA model was used.

Preparation of Sulfate Loaded TiO_2. The catalyst with TiO_2–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 dropwise 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-}.

Preparation of Quinoxaline and Dipyridophenazine Derivatives. To a mixture of *o*-phenylenediamines (1 mmol) and 1,2-dicarbonyl compound (1 mmol) in dry media, 0.1 g of TiO_2–SO_4^{2-} was added and the mixture was irradiated in a microwave oven at 480 W for 1 min. Completion of the reaction was tested by thin layer chromatography (TLC). After completion of the reaction, ethyl acetate 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 was obtained. Then it 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. A variety of substituted 1,2-phenylenediamines were condensed with benzil and 1,10-phenanthroline-5,6-dione. The catalyst separated can be reused.

2,3-Diphenylquinoxaline (3a): Mp 125–126 °C; IR (KBr): ν/cm^{-1} 3055, 2921, 1542, 1344, 768, 696; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.20 (dd, 2H, $J = 3.50$, 6.50 Hz), 7.80 (dd, 2H, $J = 3.50$, 6.50 Hz), 7.54 (m, 4H), 7.34 (m, 6H); ^{13}C NMR ($CDCl_3$): aromatic carbons are observed at δ 128.26, 128.80, 129.21, 129.74, 129.76, 129.84, 129.95, 139.10, 141.25, and 153.49 (C=N); GC-MS: $m/z = 282.3$ (M^+).

Dipyrido[3,2-*a*:2′,3′-*c*]phenazine (4a): Mp 246–247 °C; IR (KBr): ν/cm^{-1} 3073, 2852, 1577, 1498, 1415, 1361, 1337, 739, 669; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (d, 2H, $J = 6.50$ Hz), 9.28 (d, 2H, $J = 3.00$ Hz), 8.37 (dd, 2H, $J = 3.50$, 6.50 Hz), 7.94 (dd, 2H, $J = 3.50$, 6.50 Hz), 7.81 (dd, 2H, $J = 4.50$, 8.00 Hz); ^{13}C NMR ($CDCl_3$): aromatic carbons are observed

Table 1. Comparison of Condensation Reaction of *o*-Phenylenediamine and Benzil in the Presence of Different Catalysts

Entry	Solvent	Reaction conditions[a)]	Time/min	Yield	Reference
1	Ethanol/H_2O	$Ga(OTf)_3$/RT	5/30	>99/85	10
2	H_2O	montmorillonite K10/RT	2.5 h	>99	11
3	MeOH	SA/RT	5	>99	12
4	MeOH/H_2O	$CuSO_4 \cdot 5H_2O$/RT	5/15	97/96	13
5	Acetic acid	L-proline/RT	5	96	14
6	DMSO	I_2/RT	35	95	15
7	CH_3CN	I_2/RT	3	98	16
8	CH_3CN	Ni nanoparticle/RT	20	96	17
9	Ethanol/H_2O	CSA/RT	60 min/2.3 h	93/72	18
10	Ethanol	SSA/RT	15	98	19
11	Ethanol/H_2O	TiO_2–P25–SO_4^{2-}/RT	5/15	98/90.4	28
12	Ethanol/H_2O	TiO_2–SO_4^{2-}/RT	5/10	99.2/97.3	23
13	H_2O–CH_3CN	Zn^{2+}–montmorillonite K10/RT	2.5 h	89	20
14	Solvent free	Acidic alumina/heating to 80 °C	2	96	21
15	MeOH	Acetic acid/MW	5	99	22
16	Solvent free	Sulfated TiO_2/MW	1	99	present work

a) SA: sulfamic acid, CSA: cellulose sulfuric acid, SSA: silica sulfuric acid, RT: room temperature, MW: microwave irradiation.

at δ 124.14, 127.61, 129.56, 130.66, 133.78, 141.16, 142.51, 148.44 (C=N of pyridine ring) and 152.55 (C=N of phenazine ring); GC-MS: $m/z = 282.1$ (M^+).

Results and Discussion

Condensation of *o*-phenylenediamine (**1a**) with benzil (**2a**) in the presence of TiO_2–SO_4^{2-} under microwave irradiation (480 W) for 1 min in dry media gave 99% yield of quinoxaline **3a** (Table 1, Entry 16). Structure of this product was confirmed by spectral and GC-MS data. Only 40% product was obtained when a mixture of **1a** (1 mmol) and **2a** (1 mmol) was irradiated in a microwave oven (480 W) for 1 min, without solvent and catalyst. Efficiencies of the condensation reaction of **1a** and **2a** with different catalysts and reaction conditions are compared in Table 1. It indicates clearly that our method is most efficient and simple when compared to the previously reported methods for the synthesis of quinoxaline derivatives.

Encouraged by the remarkable results obtained with the above reaction conditions and in order to show the generality and scope of this new protocol, we used various substituted 1,2-phenylenediamines and the results obtained are summarized in Table 2. To check the versatility of this method, we also studied the condensation of **1a** with 1,10-phenanthroline-5,6-dione (**2b**) (Scheme 1) under the same conditions and the product dipyrido[3,2-*a*:2′,3′-*c*]phenazine (**4a**) (Table 3) was obtained in excellent yield (99%) within 1 min. The structure of this product was also confirmed by spectral and GC-MS data. All the reactions with substituted 1,2-diamines proceeded very cleanly under microwave irradiation and no undesirable side-reactions were observed, although the yields were highly dependent on the substituents. Results in Tables 2 and 3 show that electron-donating groups at the phenyl ring of 1,2-diamine favored the formation of product (Table 2, Entry 2; Table 3, Entry 2), whereas, electron-withdrawing groups such as fluoro, chloro, and carboxy decrease the yield slightly (Table 2, Entries 3–5; Table 3, Entries 3–5). Even substrates bearing a strong electron-withdrawing NO_2 group gave a good yield in 8/9 min (Table 2, Entry 6, 85.0% and Table 3, Entry 6, 87.0%). But at room temperature this nitro-substituted **1a** gave only 25% yield in 120 min[21] with TiO_2–SO_4^{2-} in ethanol. Higher efficiency even with the substrate bearing electron-withdrawing groups makes this method applicable for all kind of substrates. 2,3-Diaminopyridine and aliphatic diamine (ethylenediamine) also gave good yields in 3/4 min (Table 2, Entries 7 and 8; Table 3, Entries 7 and 8) under microwave irradiation.

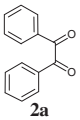
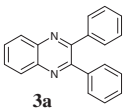
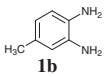
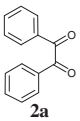
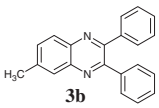
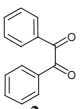
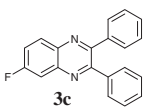
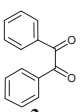
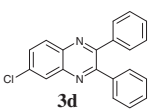
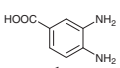
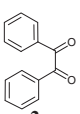
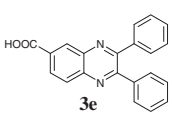
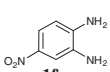
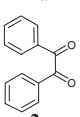
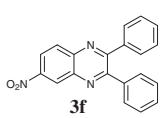
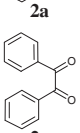
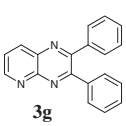
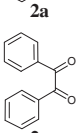
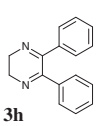
Morphology of 5 wt % TiO_2–SO_4^{2-} used for the synthesis has been analyzed by HR-TEM and AFM. HR-TEM images were taken at two different magnifications (Figures 1a and 1b). Figure 1b reveals the globular structure (round-shaped particle). It is also seen from Figure 1a that some of the particles are slightly corroded by sulfuric acid and this may be due to dissolution of TiO_2 by sulfuric acid. In AFM images (Figures 2a and 2b), circled regions of TiO_2–SO_4^{2-} also indicate the corrosion on TiO_2. This confirms the presence of sulfate in the catalyst. This corrosion is absent in the case of prepared TiO_2 (without sulfate) (Figures 2c and 2d).

As this catalyst is acidic, this reaction is likely to follow the reported mechanism of acid-catalyzed condensation reactions.[11,23] This mechanism involves the complexation of TiO_2–SO_4^{2-} with the diketone by acting as an acid and also playing a complex role in promoting the dehydration. The possibility of recycling the catalyst (TiO_2–SO_4^{2-}) was examined for the reaction of **1a** and **2a**. 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 up to fifth run 98.0%.

Conclusion

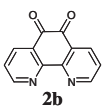
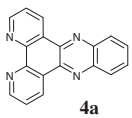
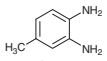
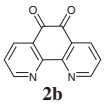
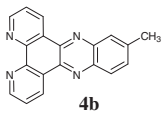
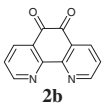
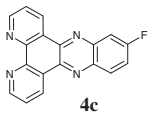
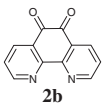
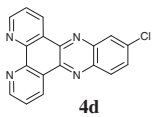
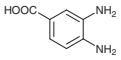
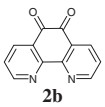
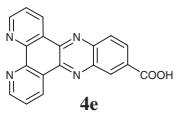
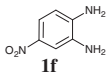
We successfully developed a simple, efficient, eco-friendly, and solvent-free method for the synthesis of quinoxaline and dipyridophenazine derivatives from various 1,2-diamines using TiO_2–SO_4^{2-} as catalyst under microwave irradiation.

Table 2. Quinoxaline Derivatives from Different 1,2-Diamines and 1,2-Diketone (Benzil) Catalyzed by TiO_2–SO_4^{2-} under Microwave Irradiation

Entry	1,2-Diamine	1,2-Diketone	Product	Time /min	Yield[a] /%
1	 **1a**	 **2a**	 **3a**	1	99.0
2	 **1b**	 **2a**	 **3b**	2	99.0
3	 **1c**	 **2a**	 **3c**	3.5	98.0
4	 **1d**	 **2a**	 **3d**	3.5	97.0
5	 **1e**	 **2a**	 **3e**	7	87.0
6	 **1f**	 **2a**	 **3f**	9	85.0
7	 **1g**	 **2a**	 **3g**	4	94.0
8	 **1h**	 **2a**	 **3h**	3.5	95.0

a) Yields with respect to 1,2-diamine.

Table 3. Dipyridophenazine Derivatives from Different 1,2-Diamines and 1,2-Diketone (1,10-Phenanthroline-5,6-dione) Catalyzed by TiO_2–SO_4^{2-} under Microwave Irradiation

Entry	1,2-Diamine	1,2-Diketone	Product	Time /min	Yield[a] /%
1	 **1a**	 **2b**	 **4a**	1	99.0
2	 **1b**	 **2b**	 **4b**	2	99.0
3	 **1c**	 **2b**	 **4c**	3	98.0
4	 **1d**	 **2b**	 **4d**	3	98.0
5	 **1e**	 **2b**	 **4e**	6	89.0
6	 **1f**	**2b**	**4f**	8	87.0
7	**1g**	**2b**	**4g**	3.5	95.0
8	**1h**	**2b**	**4h**	3	96.0

a) Yields with respect to 1,2-diamine.

Figure 1. HR-TEM images of TiO_2–SO_4^{2-}: a) 100 nm (⟹: corroded), b) 200 nm (⟹: globular or round-shaped particle).

HR-TEM and AFM analyses reveal a globular structure of the catalyst and a slight corrosion of TiO_2 by sulfate. Lewis acidity is increased by sulfate loading and hence, this reaction follows the mechanism of acid-catalyzed condensation. This method has the following advantages: 1) an inexpensive, green and reusable catalyst; 2) high product yield under mild conditions; 3) no solvent is needed. These advantages make this method a green chemical process for the preparation

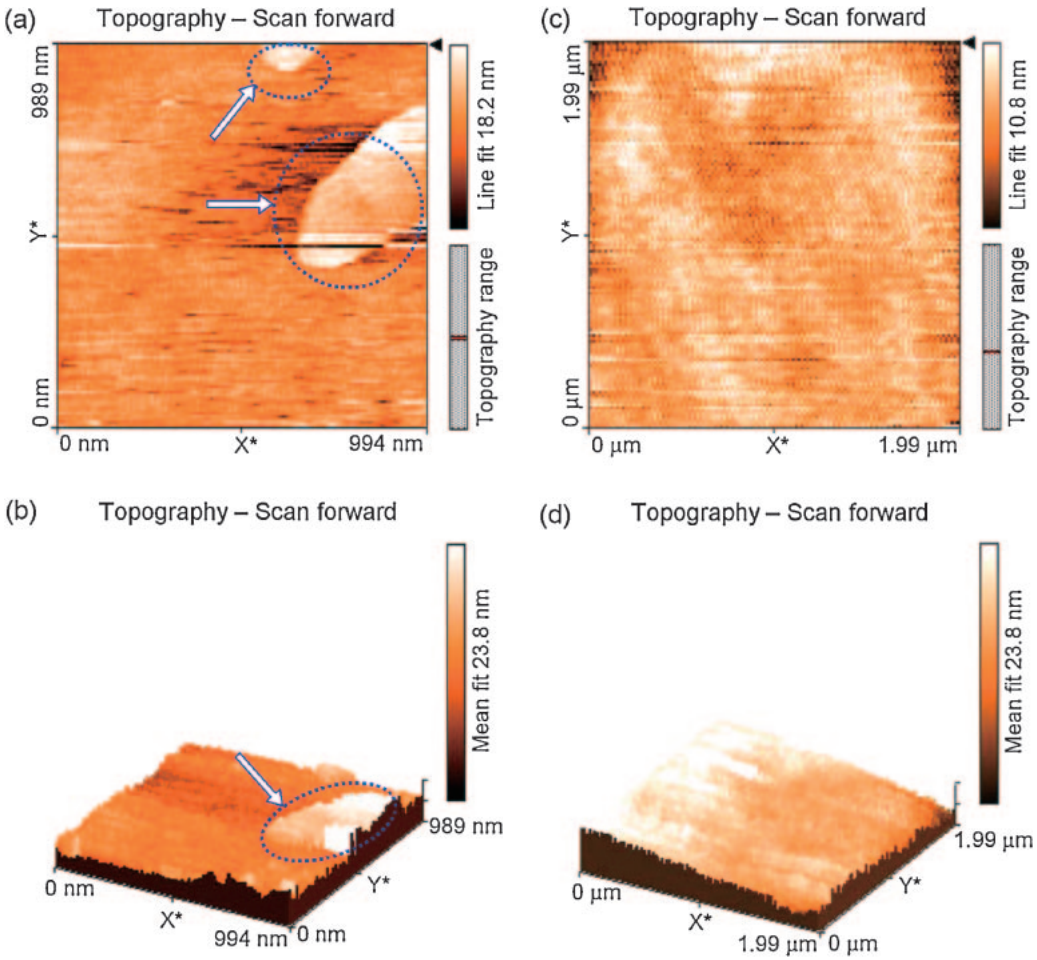


Figure 2. AFM images of a) TiO_2–SO_4^{2-} 2D image (⟹: corroded), b) TiO_2–SO_4^{2-} 3D image (⟹: corroded), c) prepared TiO_2 2D image, and d) prepared TiO_2 3D image.

of quinoxalines and dipyridophenazines. We believe this novel methodology will find wide applications in organic synthesis.

One of the authors M.S. is thankful to CSIR, New Delhi for financial support through research grant No. 21(0799)/10/EMR-II. One of the authors B.K. is thankful to CSIR, New Delhi, for the award of Senior Research Fellowship.

References

1 R. S. Varma, *Green Chem.* **1999**, *1*, 43.
2 G. Sakata, K. Makino, Y. Kurasawa, *Heterocycles* **1988**, *27*, 2481.
3 A. Monge, J. A. Palop, J. C. Del Castillo, J. M. Caldero, J. Roca, G. Romero, J. Del Rio, B. Lasheras, *J. Med. Chem.* **1993**, *36*, 2745.
4 Y. B. Kim, Y. H. Kim, J. Y. Park, S. K. Kim, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 541.
5 Z. Wu, N. J. Ede, *Tetrahedron Lett.* **2001**, *42*, 8115.
6 J. E. Dickeson, L. A. Summers, *Aust. J. Chem.* **1970**, *23*, 1023.
7 A. E. A. Porter, in *Comprehensive Heterocyclic Chemistry*, ed. by A. R. Katritsky, C. W. Rees, Pergamon, Oxford, **1984**, p. 157.
8 M. Yamada, Y. Tanaka, Y. Yoshimoto, S. Kuroda, I. Shimao, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1006.
9 D. J. Brown, *Quinoxalines: Supplement II* in *The Chemistry of Heterocyclic Compounds*, ed. by E. C. Taylor, P. Wipf, John Wiley & Sons, New Jersey, **2004**.
10 J.-J. Cai, J.-P. Zou, X.-Q. Pan, W. Zhang, *Tetrahedron Lett.* **2008**, *49*, 7386.
11 T.-k. Huang, R. Wang, L. Shi, X.-x. Lu, *Catal. Commun.* **2008**, *9*, 1143.
12 H. R. Darabi, S. Mohandessi, K. Aghapoor, F. Mohsenzadeh, *Catal. Commun.* **2007**, *8*, 389.
13 M. M. Heravi, Sh. Taheri, Kh. Bakhtiari, H. A. Oskooie, *Catal. Commun.* **2007**, *8*, 211.
14 M. M. Heravi, M. H. Tehrani, Kh. Bakhtiari, H. A. Oskooie, *Catal. Commun.* **2007**, *8*, 1341.
15 R. S. Bhosale, S. R. Sarda, S. S. Ardhapure, W. N. Jadhav, S. R. Bhusare, R. P. Pawar, *Tetrahedron Lett.* **2005**, *46*, 7183.
16 S. V. More, M. N. V. Sastry, C.-C. Wang, C. F. Yao, *Tetrahedron Lett.* **2005**, *46*, 6345.
17 A. Kumar, S. Kumar, A. Saxena, A. De, S. Mozumdar, *Catal. Commun.* **2008**, *9*, 778.
18 A. Shaabani, A. H. Rezayan, M. Behnam, M. Heidary, *C. R. Chim.* **2009**, *12*, 1249.
19 S. Ahmad, M. Ali, *Chin. J. Chem.* **2007**, *25*, 818.
20 A. Dhakshinamoorthy, K. Kanagaraj, K. Pitchumani,

Tetrahedron Lett. **2011**, *52*, 69.
21 M. Jafarpour, A. Rezaeifard, M. Danehchin, *Appl. Catal., A* **2011**, *394*, 48.
22 Z. Zhao, D. D. Wisnoski, S. E. Wolkenberg, W. H. Leister, Y. Wang, C. W. Lindsley, *Tetrahedron Lett.* **2004**, *45*, 4873.
23 B. Krishnakumar, R. Velmurugan, S. Jothivel, M. Swaminathan, *Catal. Commun.* **2010**, *11*, 997.
24 B. Krishnakumar, R. Velmurugan, M. Swaminathan, *Catal. Commun.* **2011**, *12*, 375.
25 K. Bougrin, A. Loupy, M. Soufiaoui, *J. Photochem. Photobiol., C* **2005**, *6*, 139.
26 Y. Ju, R. S. Varma, *Org. Lett.* **2005**, *7*, 2409.
27 G. W. Kabalka, L. Wang, V. Namboodiri, R. M. Pagni, *Tetrahedron Lett.* **2000**, *41*, 5151.
28 B. Krishnakumar, M. Swaminathan, *J. Organomet. Chem.* **2010**, *695*, 2572.
29 K. Arata, M. Hino, *Mater. Chem. Phys.* **1990**, *26*, 213.
30 K. Arata, *Appl. Catal., A* **1996**, *146*, 3.
31 S. K. Samantaray, K. M. Parida, *J. Mater. Sci.* **2003**, *38*, 1835.
32 A. P. Kulkarni, D. S. Muggli, *Appl. Catal., A* **2006**, *302*, 274.