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Chemoselective sulfoxidation by H_2O_2 or HNO_3 using a phosphate impregnated titania catalyst

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ABSTRACT

A variety of organosulfur compounds have been selectively oxidized to the corresponding sulfoxides by either H_2O_2 or HNO_3 using a newly developed solid acid catalyst composed of 84.5% of TiO_2 and 15.5% of $[Ti_4H_{11}(PO_4)_9]\cdot nH_2O$ ($n = 1–4$). The chemoselective oxidation of sulfides in the presence of vulnerable groups such as –CN, –C=C–, –CHO, or –OH, as well as sulfoxidation of substrates like benzothiazole, glycosyl sulfide, and dibenzothiophenes is some of the important attribute of the protocol. Nitric acid, under the present experimental conditions, brings about relatively better selectivity than hydrogen peroxide.

Selective oxidation of organic sulfides to sulfoxides is one of the key reactions in the domain of organic oxidation chemistry especially because of the potential use of sulfoxides as synthetic intermediates for construction of many chemically and biologically active molecules including therapeutic agents such as antiulcer, antibacterial, antifungal, and antihypertensive.[1] Thus, selective oxidation of sulfides has received continued attention leading to the development of a number of reagents,[2–4] acids,[5] transition metal catalysts like titanium,[6–11] vanadium,[12] iron,[13] molybdenum,[14] tungsten,[15] manganese,[16] copper,[17,12c] and zeolite-based catalysts,[18,19] to mention a few. While all these are important developments, there are several difficulties associated with the protocols being used in practice, viz., non-selectivity, over oxidation, cost effectiveness, and toxicity of catalysts. In view of the above, research in this area continues in the quest of newer catalysts and protocols for selective sulfoxidation under easy operational conditions.

Recently, Shi et al. have reported self-catalyzed sulfoxidation reaction at high temperature (i.e., 70 °C) with hydrogen peroxide.[20] Although it is a green process, it does not work well for low volatile sulfides, for example, dimethyl sulfide (bp. 38 °C). Moreover, Gomez et al. conducted a comparative study with different oxidant and support to delineate the role of support in selectivity of sulfoxidation, according to which acid support (amberlyst) gave sulfoxide selectively, basic support (basic alumina) increased the proportion of sulfone formed.[2]

A great variety of titanium-containing catalysts were tested for sufoxidation reaction with better efficiency as well as selectivity.[6] Enantioselective sulfoxidation was achieved with titanium-chiral ligand complex.[8] Very recent report suggests that nanosized-TiO_2 can catalyze the oxidation of sulfide to sulfone with high yield.[9] Of particular relevance here are the titanium-based zeolite catalysts. The selectivity of the catalyst depends on the support or its surrounding environment. For instance, titanium silicates-1(TS-1) and TS-2 gave a mixture of sulfoxides and sulfones (e.g., $PhSOMe/PhSO_2Me = 78:22$), whereas Ti-beta and Ti-MCM-41 gave approximately 2:1 ratio. In addition, Ti-beta catalyst was more active than TS-1 in the oxidation of dibutyl sulfide to dibutyl sulfone providing 78% and 20.5% conversion, respectively.[6] Other titanium-containing zeolites are found to give moderate to high yield of sulfoxides and sulfones.

As a sequel to our endeavor in developing newer catalysts and methodologies,[4,21,22] a solid acid catalyst composed of 84.5% of TiO_2 and 15.5% of $[Ti_4H_{11}(PO_4)_9]\cdot nH_2O$ ($n = 1–4$) has been prepared by impregnating phosphate on titania.[21] In a recent study on the nitration of organic substrates using nitric acid with the same catalyst, oxidation of sulfides predominated. This provided an impetus for the present investigation. The fact that the catalyst contains both titania and phosphate, which are known to activate H_2O_2 through the formation of peroxotitanate and peroxophosphate intermediates, it is expected to be a potential catalyst for the oxidation with H_2O_2.

Reported herein are the results of chemoselective oxidation of a range of organic sulfides separately with H_2O_2 and HNO_3 catalyzed by the aforementioned catalyst. An internal comparison of the

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Table 1

Sulfoxidation of organic sulfides with H_2O_2 and HNO_3

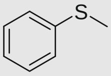
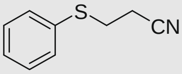
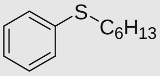
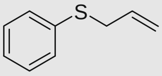
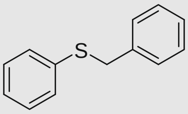
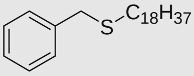
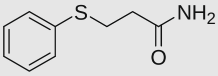
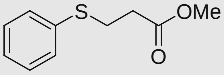
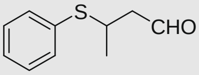
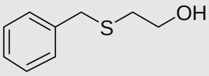
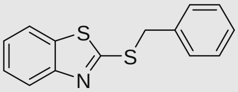
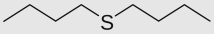
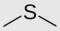
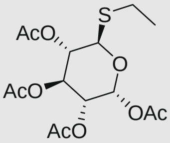
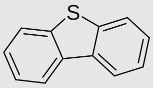
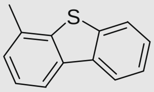
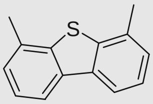
Entry	Substrate	H_2O_2		HNO_3	
		Time (h)	Yield[a] (%) sulfoxide:sulfone	Time (h)	Yield[a] (%) sulfoxide:sulfone
1		0.8	98 (95:5)	5	99 (100:0)
2		6	73 (85:15)	20	70 (90:10)
3		10	90 (98:2)	10	95 (100:0)
4		9	70 (85:15)	20	65 (95:5)
5		8, 12[d]	85, 88[d] (95:5)	45, 60[d]	90, 92[d] (98:2)
6		13	75 (95:5)	45	90 (100:0)
7		10	85 (85:15)	60	90 (98:2)
8		10	78 (90:10)	55	92 (98:2)
9[b]		2	65 (85:15)	30	58 (95:5)
10[b]		3	73 (90:10)	30	50 (95:5)
11		10	85 (79:21)	20	90 (100:0)
12		7	90 (72:28)	15	95 (100:0)
13		0.25	99 (20:80)	15	99 (95:5)
14		6	90 (95:5)	20	65 (95:5)
15		12	84 (75:25)	30	90 (100:0)[c]
16		24	77 (75:25)	90	65 (100:0)[c]

Table 1 (*continued*)

Entry	Substrate	H_2O_2		HNO_3	
		Time (h)	Yield[a] (%) sulfoxide:sulfone	Time (h)	Yield[a] (%) sulfoxide:sulfone
17		42	35 (80:20)	360	30 (100:0)[c]

[a] Isolated yield.

[b] Reaction was carried out at 0 °C.

[c] Nitrated product was observed along with sulfoxide.

[d] Reaction in 5 g scale.

results has been made in order to comment on the efficiency of the chosen oxidants. A set of our results has been also compared with those of others obtained using titanium-based catalysts to enable us comment on the efficacy of the present protocol.

Reagent grade chemicals such as titania (Qualigens, India) and 88% phosphoric acid (E. Merck, India) were used, as purchased. Dibenzothiophene (DBT), 4-methyl DBT, 4,6-dimethyl DBT were purchased from Sigma Aldrich, India. Other organic sulfides were prepared by literature procedures.

The catalyst was prepared[21] by first mixing titania with phosphoric acid (88%), in the molar ratio of TiO_2:H_3PO_4 as 1:1, in a silica boat followed by heating at 200–220 °C on a hot sand bath under stirring until the mass solidified. Heating was then discontinued and when the temperature came down to ca. 100 °C, the catalyst was transferred to a vacuum desiccator. Finally the catalyst was stored in an airtight sample vial.

In a typical experiment, to a round-bottomed flask containing a mixture of the catalyst (0.02 mmol, 1 mol %) and hydrogen peroxide (50%) (3 mmol, 0.204 mL) or nitric acid (70%) (3 mmol, 0.27 mL) in 3 mL of solvent, benzyl phenyl sulfide (2 mmol, 0.2 g) was added and stirred at room temperature for the time period specified in Table 1. While methanol was used as the solvent for hydrogen peroxide, acetonitrile was used for nitric acid oxidations. The reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethyl acetate and washed with 5% aqueous solution of sodium bicarbonate (2.5 mL) followed by water (5 mL) in the cases of nitric acid oxidations, whereas for those of the hydrogen peroxide oxidation washing with water alone was done. The ethyl acetate extract was dried with anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography on silica gel using *n*-hexane and ethyl acetate (95:5) as eluent afforded the corresponding sulfoxide and sulfone in the ratio 95:5 and 98:2, respectively, for hydrogen peroxide and nitric acid with the overall yields of 85% and 90%.

Based upon the results of trial runs, the reaction conditions were optimized with 1 mol % of the catalyst and 1.5 mmol of oxi-

Table 3
Oxidation of benzyl phenyl sulfides with H_2O_2 and HNO_3

Entry	Reagent	Time (h)	Yield (%)
1	H_2O_2	36	25
2	HNO_3	3	65

Table 4
Oxidation of benzyl phenyl sulfide with different catalysts

Entry	Catalyst	H_2O_2		HNO_3	
		Time (h)	Yield (%)	Time (min)	Yield (%)
1	TiO_2	36	65	120	75
2	H_3PO_4	17	70	90	76
3	Catalyst	8	85	45	90

Table 2
Comparative reactivity of benzyl phenyl sulfide and sulfoxide

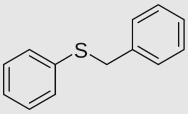
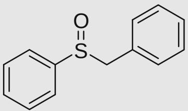
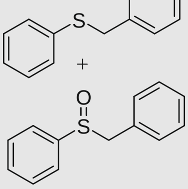
Entry	Substrate	H_2O_2		HNO_3	
		Time (h)	Sulfoxide:sulfone	Time (min)	Sulfoxide:sulfone
1		8	95:5	45	98:2
2		24	25:75	80	15:85
3		8	91:9	45	98:2

Table 5
Comparison of the catalyst with other titanium-based catalysts in terms of efficiency and selectivity of methyl phenyl sulfide oxidation with H_2O_2

Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)	Ratio[SO:SO_2]	Ref.
TS-1	Acetone	Reflux	2.5	98	—	19,24
TS-2	Acetone	Reflux	2.5	98	78:22	10
Ti-β	Acetone	rt	2	85	—	11
Ti-MCM-41	Acetonitrile	rt	5	99	83:17	19b
Ti(IV)-glycolate	—	rt	2	71	86:14	7b
TiO_2-VO(acac)$_2$	DCM	rt	1.5	99	97:3	23
Present-catalyst	MeOH	rt	0.8	98	95:5	—

dant against 1 mmol of benzyl phenyl sulfide either in acetonitrile for HNO_3 or in methanol in the case of H_2O_2. Whereas acetonitrile was found to work well for HNO_3, methanol appeared to be a better solvent for the H_2O_2 oxidations. Coordination of alcohol to the active site of titanium (cf. Alkoxy-Ti) presumably increases the electrophilicity of the coordinated peroxy oxygen atom thereby favoring the nucleophilic attack of the organic substrate, ultimately facilitating the overall oxidation.[23] The inherent acidity of the catalyst might have further enhanced the reactivity.

Structurally diverse sulfides were subjected to oxidation under the optimized reaction conditions and the results are summarized in Table 1. Evidently, both the oxidants worked well though HNO_3 appeared to be comparatively better in terms of both selectivity and efficiency (Table 1). The reagent systems chemoselectively oxidize sulfides in the presence of other oxidation prone functional groups such as –CN, –C=C–, –CHO, and –OH (Table 1, entries 2, 4, 9, and 10). The protocol works efficiently in oxidizing 2-(benzylthio)benzothiazole to afford the exocyclic sulfoxide (Table 1, entry 11). Notably, neither sulfur nor nitrogen in the heterocycle ring nor the benzylic position was affected in the process. Importantly, this product is comparatively easily biodegradable than the substrate.[24] Glycosyl sulfide is easily oxidized to the corresponding sulfoxide (Table 1, entry 14), which is used in chemical glycosylation.[25]

Though the oxidation of refractory sulfides is rather difficult, the present protocol, however, oxidizes dibenzothiophene (DBT) (Table 1, entry 15) and mono and disubstituted DBTs (Table 1, entries 16 and 17) with reasonably good success. The ease of oxidation followed the expected trend, viz. DBT > 4-methyl DBT > 4, 6-dimethyl DBT. Steric crowding on the disubstituted DBT restricting the approach of the active oxidant to sulfur is attributed to the difficulty in its oxidation. The presence of a very small amount of nitrated product was detected in each of these cases when HNO_3 was the oxidant.

The comparative reactivity of sulfide and the corresponding sulfoxide was also studied to ensure the selectivity of the catalyst (Table 2). The sulfides are more reactive than sulfoxides. The more reactive sulfide competes with the sulfoxide thereby resulting in a very low yield of sulfone.

Though hydrogen peroxide and nitric acid can themselves oxidize benzyl phenyl sulfides (Table 3, entries 1 and 2), reactions are sluggish, thereby demanding the need of catalyst for the activation.

In separate experiments, evaluation of the catalyst and its analogs was done to ensure the efficiency of the catalyst over the others and the results are presented in Table 4. These observations suggest that neither titania nor phosphoric acid alone is very effective to forward the desired reaction.

From the preparative point of view, it is noteworthy that the catalyst can be efficiently recovered by evaporating the aqueous layer and then recharging by heating on silica boat at 200–220 °C for 30 min. Indeed, the catalyst was reused with benzyl phenyl sulfide for at least four reaction cycles with consistent activity and selectivity. The reaction can be scaled up (5 g) to give good yield (Table 1, entry 5) showing its prospect for preparative scale applications.

In order to evaluate the efficiency of the catalyst, we have compared the reaction of methyl phenyl sulfide and H_2O_2 with those of a few other titanium-containing catalysts (Table 5). It is clear from the results that although the yields are similar, the reaction time in the present case is shorter and the selectivity is better than the others. In addition, the chemoselectivity appears to be relatively higher than its companion catalysts.

In conclusion, an efficient method for the selective oxidation of sulfides to sulfoxides under mild condition has been developed. The catalyst-nitric acid system oxidizes simple alkyl or aryl sulfides more efficiently and selectively than the catalyst-hydrogen peroxide system. However, latter one is preferable from the environmental point of view. These processes chemoselectively oxidize sulfur in presence of a double bond, nitrile, alcohol, aldehyde, benzylic methylene and nitrogen or sulfur atom in a heterocyclic position. Applications to the refractory sulfurs and glycosyl sulfide make the catalytic protocols more generalized. Easy work-up and separability are the other important attributes of the protocol.

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