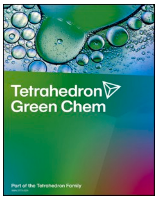
Tetrahedron Green Chem 2 (2023) 100031

Contents lists available at ScienceDirect

Tetrahedron Green Chem

journal homepage: www.journals.elsevier.com/tetrahedron-green-chem



Revisiting the role of sulfated oxides for the synthesis of pharmaceutically important heterocycles: Understanding, challenges, and future prospects

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ARTICLE INFO

Keywords:
Zirconia
Benzodiazepine
Biginelli
Redox
Catalysis

ABSTRACT

The development of sustainable catalytic processes is the requirement of the future to replace traditional protocols involving hazardous, non-green, non-benign reagents/solvents, and cost ineffectiveness. Metal and mixed metal oxides due to their redox properties make them potential substitutes for conventional homogeneous catalysts. The acidity can be enhanced further by the sulfation process to form sulfated oxides representing a new class of solid acid catalysts. This review is the revisiting of sulfated solid acid catalysts, with major emphasis on understanding, methods, applications, and their role in the syntheses of heterocycles of pharmaceutical importance. The present review also discusses factors affecting the acidity of the catalysts, possibilities of leaching in reaction media, methods of sulfation to arrest leaching, other challenges, and future prospects.

1. Introduction

Many industrial processes rely on solid acid catalysts for the important chemical transformations. Among various industrial sectors, solid acid catalysts have been widely used in petrochemical industries for reactions such as cracking, isomerization, and alkylation [1]. The acidity of solid acid catalysts plays a crucial role in catalysis, in particular acid-catalyzed transformations. For instance, cumene (isopropylbenzene) is produced from benzene and propene as raw materials over Y-zeolite, H-BEA (Beta structured zeolite), and MCM-22 (MCM: Mobil Composition of Matter) by Unocal, UOP Q-max, and Mobil-Raytheon respectively [2]. The mentioned class of catalysts not only finds applications in the synthesis of *fine* but also *specialty* chemicals.

Sulfuric acid is used as a catalyst for various industrial processes. However, its hazardous nature made it difficult to handle on a large scale. There are numerous attempts to replace mineral acids with heterogeneous catalysts. Solid acid catalysts are reusable and greener compared to homogeneous acids (sulfuric and other acids). Metal oxides (MOs) are used as acid catalysts [3] largely by industries after zeolites. Their redox properties, tunable acidity, basicity, and higher surface area (SA) make them promising candidate for the acid catalyzed transformations. In case of mixed metal oxides (MMOs), acidity/basicity can be altered by the excess of charges (positive or negative) contributed by each binary oxide. MMOs are of two kinds, solid solutions (non-stoichiometric) and true mixed metal oxides (stoichiometric, e.g., perovskites, spinel, etc.), latter is widely explored in nuclear-research, ceramics, electronics and importantly catalysis [3–8]. Properties of MMOs are far different than individual MOs and can be well understood with the Tanabe's model (titania-zirconia mixed oxide) [9]. Tanabe's model explained generation of new acidic and basic sites in case of TiO_2–ZrO_2 (Fig. 1 *Left*). Though individual oxides have fewer weakly acidic/basic sites, however, TiO_2–ZrO_2 displayed presence of high amount of strongly acidic/basic sites along with high thermal stability, SA, and mechanical strength. In general, acidic/basics strengths of individual MOs can be enhanced by forming MMOs (Fig. 1 *right*). Moreover, the acidic strength can be enhanced further by the sulfation.

This review, majorly focuses on the basic understanding of sulfation, sulfated oxides, sulfated mixed metal oxides, their preparations, and applications as catalysts for the syntheses of pharmaceutically important heterocycles. To the best of our understanding, this will be the first study to collect abundant findings of the syntheses of heterocyclic compounds catalyzed by sulfated metal and mixed metal oxides.

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https://doi.org/10.1016/j.tgchem.2023.100031
Received 14 August 2023; Received in revised form 10 November 2023; Accepted 22 November 2023

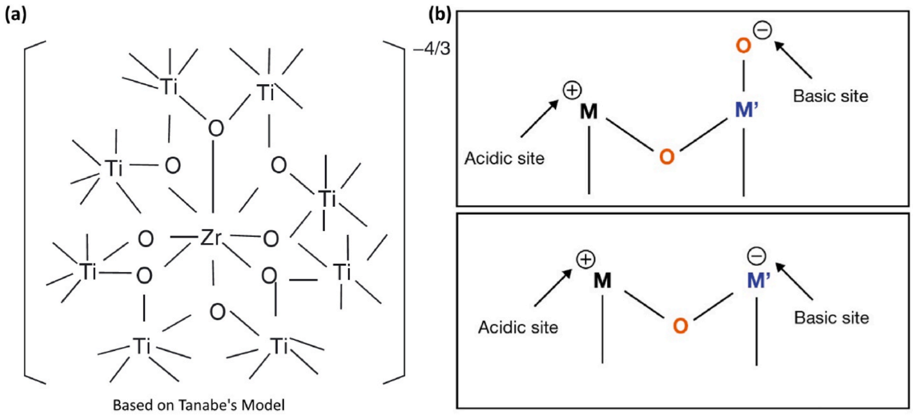


Fig. 1. (a) Generation of new acid–base sites in TiO_2–ZrO_2 oxides based on Tanabe's model; (b) Possible acidic and basic sites in case of mixed metal oxides [3,9].

2. Sulfation

Holm and Bailey in 1962 patented sulfate anion modified zirconia gel exhibiting excellent catalytic activity for the isomerization of hydrocarbons (*n*-butane, *n*-pentane, etc.) compared to commercially available catalyst [10]. It was observed that a typical treatment of zirconia with ammoniums sulfate or sulfuric acid could develop strong acidic sites that could isomerize *n*-butane to isobutane at room-temperature [11]. Another studies showed that the significant activity was attributed to highly acidic nature of sulfated zirconia (SZ) compared to sulfuric acid with Hammett acidity of $-14.52 \leq H_o$ [12]. However, the superacidic nature of SZ is debatable based on used methods for its measurement and questioned by few researchers in the field [13–15].

Characteristics of any sulfated catalysts found to be influenced by various factors such as metal precursor, precipitant, sulfating agent, method of preparation, calcination temperature, among others. However, sol-gel and precipitation-impregnation are the most widely used preparation methods, where the former and the latter are one and two step methods respectively. Characterization of the sulfated oxides, helped to elucidate the structure of the material (Table 1), understand, and compare their catalytic activities. Techniques used for the characterization include, X-ray diffraction (XRD), Fourier Transform Infrared Spectroscopy (FTIR), Raman Spectroscopy, X-ray Photoelectron Spectroscopy (XPS), Thermal Analysis, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Ultraviolet–visible Diffused Reflectance Spectroscopy (UV–vis DRS), and the Potentiometric Titration method. Acidity measurements of the sulfated oxides is quite tricky compared to liquid acids due to surface heterogeneity and accessibility of acidic sites to the probe base molecule [16].

Between above mentioned preparation methods, sol-gel has gained popularity due to several advantages such as (a) possibility to control the shape and size of resulting material particles (b) low temperature requirement compared to other methods (c) high chemical homogeneity, among others [17–19]. Typically, in sol-gel, metal alkoxide is hydrolysed and subsequently condensed in alcohol (solvent) to for alcogel (polymeric-oxide network) followed by solvent removal to yield xerogel with reduced surface area. Removal of solvent under supercritical condition forms aerogel which avoid liquid-vapor interface as observed during xerogel formation [20]. For instance, Ward et al., reported aerogel SZ synthesis in one step wherein, sulfuric acid was mixed with Zr-precursor (Zirconium *n*-propoxide) in 1-propanol which further reacted with nitric acid and water to yield cogel followed by supercritical drying with CO_2 to form SZ aerogel [21]. Melada et al., prepared SZ using similar one step method, where the obtained gel was dried and calcined at various temperatures and studied the effect of calcination temperature, water/metal alkoxide nature, etc. on the surface area [22]. Alves-Rosa et al., reported similar material by sol-gel method using surfactants (Pluronic, SDS, etc.) and air-liquid foam as pore templates. It was observed that type of surfactant affected the final SA of the sample after the calcination (600 °C) [23]. Tichit et al., had observed the effect of concentration of sulfuric acid on SA of sample prepared from Zr $(OC_3H_7)_4$ calcined at 650 °C [17].

SZ can also be prepared by two step preparation method i.e.,

Table 1
Structural elucidation of sulfated zirconia by various investigators.

Sr. No.	Proposed by	Technique used for structural elucidation	Sulfate IR bands	Ref.
1	K. Arata (1990)	XPS and IR spectra	Absorption bands at 980–990, 1040, 1130–1150, and 1210-1230 cm^{-1}, which are assigned to the bidentate sulfate coordinated to metal elements	[33]
2	F. Babou et al. (1994)	Infrared study, Quantum chemistry calculations using ab initio methods	IR bands at 1229, 1153, 1043 and 1000 cm^{-1}	[34]
3	D. A. Ward and E. I. Ko (1994)	in situ and ex-situ DRIFT and XRD	1137, 1187, 1064, and 996 cm^{-1}	[21]
4	T. Jin et al. (1986)	IR spectra	I.R. bands at 1390, 1190, 1020, and 930 cm^{-1} in the SO stretching frequency region	[35]
5	C. Morterra et al. (1994)	I.R. data of adsorbed pyridine in the dehydration and rehydration	δ_{HOH} mode at nearly ≈3590, ≈3250, and ≈3170 cm^{-1} suggests $[H_3O]^+$ (oxonium) groups 1450-850 cm^{-1} contains the S-0 stretching vibrations of surface sulfate species	[36]
6	M. Bensitel et al. (1988)	IR spectra	250 μmol/g SO_2, IR bands near 1355 and 1370 cm^{-1}	[32]
7	M. Hino et al. (2006)	XPS and thermal analysis	The spectra of S 2p, binding energies are 168.9 and 169.2 eV for SO_4/ZrO_2.	[37]
8	A.I.M. Rabee et al. (2017)	FTIR and XPS	$\nu_{S\text{-}O}$ and $\nu_{S]O}$, at bands at 1142, 1040, and 960 cm-1 and 1240 and 1076 cm^{-1}	[38]
9	A. Clearfield et al. (1994)	IR spectra	Strong IR band at 1370 cm^{-1} which has been assigned to an asymmetric stretching vibration of S]O. The adsorption of pyridine caused a large shift in the S]O band to 1330 cm^{-1}	[39]

precipitation of Zr precursor to hydroxide followed by impregnation method. Type of Zr-precursor used for the precipitation showed considerable effect on final texture of the material, SA as well as total acidity of the sample. In most of the results, higher concentration of sulfuric acid led to the formation of high SA sulfated zirconia samples [24–27]. Sulfation was also employed by few researchers using incipient wetness [28,29] and dry-kneading [30]. Hino and Arata claimed the synthesis of higher super acid catalysts (SZs) with strength of $H_o \leq -16.4$, compared to the SZ prepared using kneading of zirconium hydroxide with ammonium sulfate as sulfating agent and chlorides of metals (M = Pt, Pd, Rh, Ir, Rh and Ru) [30]. SO_2Cl_2, SO_2, H_2S and CS_2 are other sources of sulfur, converting to sulfate species during catalyst preparation (calcination and pre-treatment) [26,31,32].

Most of the investigators, reported higher SA of the SZ due to high concentration of sulfating agent. Characterization techniques such as FTIR, XPS, Raman, and ^1H MAS NMR played vital role to investigate and propose the structures of sulfated zirconia (Fig. 2). In FTIR, SZ display IR bands at 1216-1210, 1134–1140, 1057–1060, and 990 cm^{-1} indicating interaction of bidentate sulfate ion with Zr^{4+} species when the sulfation was carried out using sulfuric acid. In case of sulfating agents such as CS_2, SO_2, and H_2S, similar bands between 1400 and 900 cm^{-1} were appeared. It confirmed that the formation of sulfate species is regardless of employed sulfating agent. Moreover, asymmetric vibrations of S]O stretching displayed bands in the region 1364-1390 cm^{-1} attributed to the sulfate species linked with zirconia under dehydrated state.

Catalytic applications of sulfated materials are due to their surface acidity often measured using ammonia TPD. However, acidic strength measurement using NH_3-TPD is quite difficult to analyze sulfated samples due to (a) diffusion of desorbed species (b) re-adsorption on active sites (c) decomposition at elevated temperature, etc. Therefore, Argon TPD is recommended while evaluating surface acidity of superacids/sulfated samples [40]. For superacids, potentiometric titration have also been successfully employed in the past. For instance, Vazquez et al., reported acidity of the silica-supported heteropolyacids (HPAs) using 0.05 N *n*-butylamine in acetonitrile (*ACN*) at 0.05 mL/min. Interpretation of the results are as follows (a) if, initial electrode potential E > 100 mV: indicates very strong acidic sites; (b) if, 0 > E > 100 mV: indicates strong acidic sites; (c)if, −100 < E < 0 mV indicates weak acidic sites, and (d) if, E < −100 mV indicates very weak acidic sites [41].

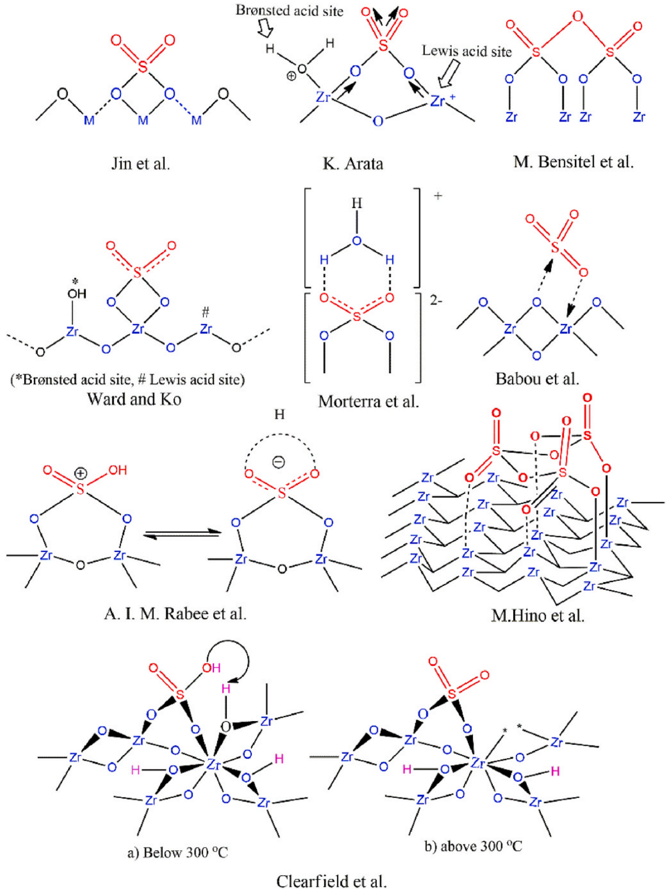


Fig. 2. Various proposed structures of sulfated zirconia (SZ).

3. Catalytic applications

In 2019, whole world was affected by Covid-19 crisis. wherein, the efforts made by researchers in the development of drugs and vaccines played a pivotal role in overcoming the situation. Structural skeleton of most of the drugs are composed of heterocyclic structures. Many heterocyclic compounds can be synthesized easily in one pot by multicomponent reaction over solid acid-base catalyst or other class of materials [42,43]. Among various sulfated oxides (acidic catalysts), SZ is now commercially available with Sigma-Aldrich and FUJIFILM Wako Pure Chemical Corporation. It is the most explored as a catalyst for heterocycles syntheses application due to its robust nature. Sulfated oxide This section deals with the catalytic applications and role of sulfated zirconia (majorly) and other sulfated metal and mixed metal oxides in synthesis of pharmaceutically important heterocycles.

3.1. *Synthesis of 1,5-benzodiazepine derivatives*

Benzodiazepines are pharmaceutically important due to their applications as analgesic, anticonvulsant, anti-inflammatory, hypnotic, anti-depressive and sedative agents [44]. 1,5-benzodiazepine and their derivatives are potential intermediates in the syntheses of fused heterocyclic derivatives of the same (oxazino-, oxadiazolo-, triazolo-, furano-benzodiazepines) [45,46]. In general, synthesis of benzodiazepines is reported by the condensation of *o*-phenylenediamines with β-haloketones, α, *β*-unsaturated carbonyl compounds, etc. using BF_3–etherate [47], triflate [48], and in ionic liquid [49].

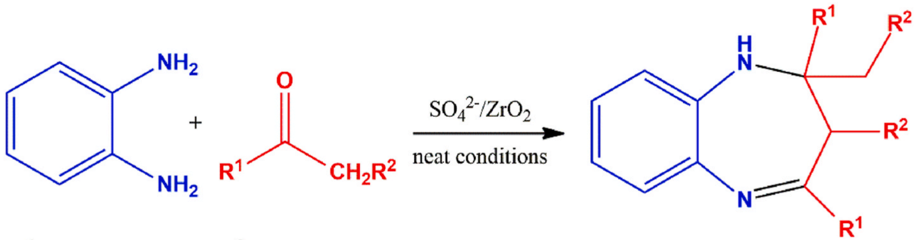
Reddy et al., reported the solvent free synthesis of 2,3-Dihydro-1H-1,5-benzodiazepines by condensing *o*-phenylenediamines with ketones over recyclable SZ providing excellent yield (80–96 %) in 2–3 h (Scheme 1) [51]. Sulfation was carried out using 0.5 M sulfuric acid and the sample after drying was subjected to calcination at 873 K/4h. Prepared SZ material displayed the formation of tetragonal phase of zirconia by XRD and XPS studies confirmed the formation of stable zirconia-sulfate species.

3.2. *Synthesis of 3,4-dihydropyrimidin-2(1H)-ones*

Dihydropyrimidines is an important class of compounds known for their medicinal as well as pharmacological applications. Dihydropyrimidines and their derivatives find applications as antibacterial, antiviral, antihypertensive, α_{1a} adrenoceptor-selective antagonists, etc. [52–56]. Monastrol, a dihydropyrimidine analogue is one of the possible leading anticancer agent with high activity for mitosis blocking by inhibiting motility of a motor protein [56,57]. Dihydropyrimidines are synthesized by multicomponent reaction between an aldehyde, *β*-keto ester and urea preferably in an acidic medium. It was developed in 1893 by Italian chemist Pietro Biginelli. Over the period of time, significant development in Biginelli reaction have been reported owing to the drawbacks in earlier process [55].

Syntheses of 3,4-dihydropyrimidin-2(1*H*)-ones have also been reported over different Lewis

Acid catalysts such as $InCl_3$ [59], $SnCl_2.2H_2O$ [60], $BF_3.OEt_2$ [61], $FeCl_3.6H_2O$ [62], $NiCl_2.6H_2O$ [62], among others [56,63,64]. It is practically difficult to separate and reuse Lewis acids multiple time with economic viability. Reddy et al., reported its synthesis from an aldehyde, β-keto ester, and urea/thiourea over SZ under solvent free conditions



R^1 = -CH_3, -CH_2-CH_3; R^2 = -CH_3, -CH_2-CH_3, -Ph;
R^1, R^2 = -Cyclohexyl

Scheme 1. Sulfated zirconia catalyzed synthesis of 1,5-benzodiazepine derivatives [50].

(Scheme 2). Sulfation reported to enhance acidity as well as SA of the final catalyst material. XRD revealed the substantial increase in the tetragonal phase after sulfation process, proved to have catalytically active acidic-sites in different reports [38,65]. In another studies, at 80 °C under solvent free conditions [66], formation of trace amount of Hantzsch product i.e., 1,4-dihydropyridines along with Biginelli as major product was observed. Notably, at 150 °C, 16–64 % of Hantzsch as major product was recorded with the declined Biginelli product. However, in reusability studies, considerable decrease in the catalytic activity was seen after first run due to the formation of monoclinic phase zirconia (confirmed by XRD). SZ was further explored for the syntheses of mentioned heterocycles under microwave (320W) and in heating mantle to check the effect microwave irradiation [67]. When the reaction was carried out over SZ/phosphotungstic acid, under solvent free MW irradiation (900 W), product formation was observed in 1–2 min [68].

3.3. *Synthesis of benzimidazoles, benzoxazoles, benzothiazoles, quinoxalines*

Benzimidazoles, benzoxazoles, benzothiazoles, and quinoxalines are the core building blocks of various pharmaceutical compounds [69–72]. Teimouri et al. screened nanostructured γ-alumina, ZnO, SZ, and ZSM-5 materials as catalysts for the syntheses of benzimidazoles by condensing *o*-Phenylenediamine with aromatic aldehydes (Scheme 3) [73]. However, in ethanol under reflux condition, the order of catalytic activity is as follows.

Nano-SZ > Nano- γ-alumina > Nano-ZnO > Nano-ZMS-5.

Highest catalytic activity was recorded for nanostructured SZ with 80–92 % yields of benzimidazoles in 45–90 min.

Among screened oxides, Nano ZnO recorded the lowest activity due to the minimal total acidity (0.315 mmol/g) from TPD [74]. However, in another report over nano SZ at 50 °C, ethanol offered best yields (70–97 %) compared to solvents like acetonitrile, dichloromethane, chloroform, etc. Blocking of active sites and deposition were found as two major reasons for the catalyst deactivation. For the reuse, catalyst was regenerated by calcination at 600 °C for 2h consistent with the literature [75]. The protocol also provided better yields for benzimidazoles and bis-benzimidazoles. Compared to SZ, more catalyst loading was required for the sulfated tin oxide catalyst (20 mol%) in water:ethanol (1:1) solvent system under reflux conditions to achieve comparable yield.

For the synthesis of benzoxazoles and benzothiazoles, 2-aminophenols or 2-aminothiophenols were condensed with aldehydes over sulfated catalysts (Scheme 4) [73].

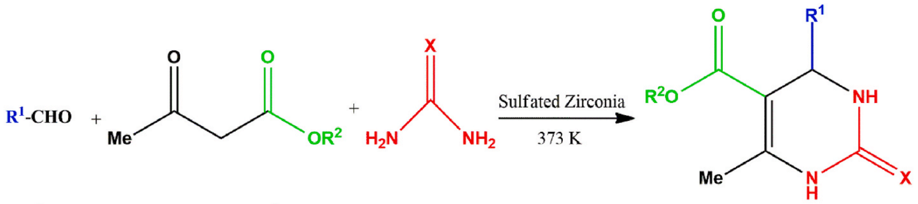
The catalytic activities of nanostructured ZnO and SZ were evaluated for the synthesis of benzoxazoles and benzothiazoles in ethanol under reflux condition, wherein, nano SZ recorded excellent activity attributed to higher acidity. The protocol was highly robust for the aldehydes with structurally diverse substituents. Among Nano-SZ, Nano- γ-alumina, Nano-ZnO, and Nano-ZMS-5, Nano-SZ recorded highest activity when screened for synthesis of quinoxalines by condensing 1,2-dicabonyls and *o*-phenylenediamines.

3.4. *Synthesis of N-fused benzimidazolo/benzothiazolo pyrimidines*

Pyrimidine derivatives are known for their medicinal properties [76–79]. Many commercially important drugs, like ceritinib (anticancer), methotrexate (anticancer and to treat arthritis), sulfadimidin (anti-urinary tract infection), etc. have pyrimidine as a core part of the structures. Nucleus with benzimidaole/benzothiazoles fused with pyrimidines are known to form basic structural skeleton of important bioactive molecules [80]. Some of old reports for the synthesis of these fused heterocycles include, reaction of *β*-diketones with 2-aminobenzimidazole [81] and $AlCl_3$ catalyzed reaction between 2-substituted benzimidazole and carbon suboxide [82].

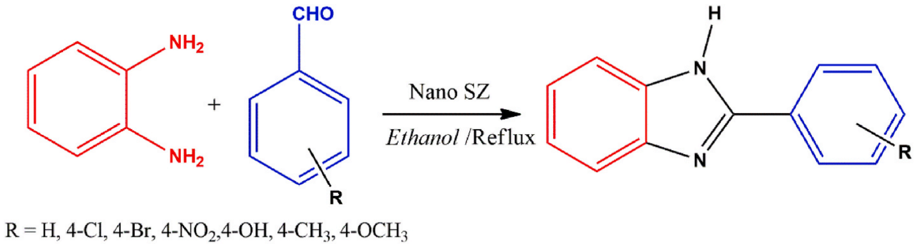
Multicomponent reactions are prominent in synthesis of heterocycles [83]. A typical multicomponent reaction between alkynes, aldehydes and amines over CuI/Ag_2CO_3 catalyst provided N-fused benzimidazolo pyrimidine compounds [84]. Mentioned catalyst lead to the formation of propargylamine intermediate which further underwent 6-*endo*-dig regioselective cyclization to yield imidazo [1,2-a] pyrimidines. However, this cascade reaction needed reflux conditions, expensive catalytic system and longer reaction time [84]. Condensation of 2-aminobenzimidazole/2-aminobenzothiazole, phenyl acetylene, and substituted benzaldehydes over sulfated copper oxide was reported by Sankarnarayanan et al. (Scheme 5) [85]. The catalytic activity of sulfated copper oxide provided excellent yields of fused heterocycles when compared with other oxides (CeO_2, ZrO_2, Y_2O_3, etc.). However, comparison of sulfated CuO was made only with non-sulfated oxides in the report.

Synthesis of both N-fused benzimidazolo pyrimidine (Scheme 5a) and N-fused benzothiazolo pyrimidine (Scheme 5b) were carried out under nitrogen atmosphere in acetonitrile (ACN). The predicted



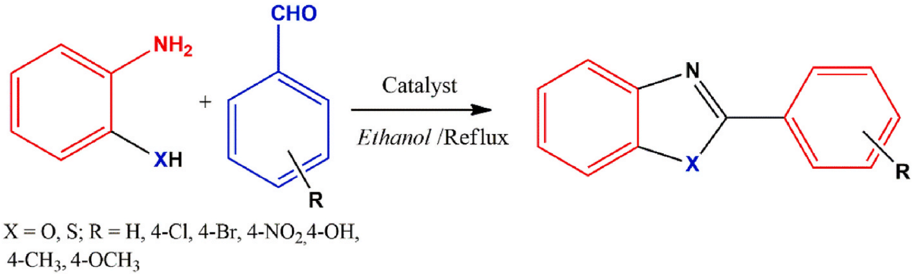
R^1 = -Ph, -Ph-NO_2, -Ph-OH; R^2 = -Me, -Et; X = O, S

Scheme 2. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones involving sulfated zirconia [58].



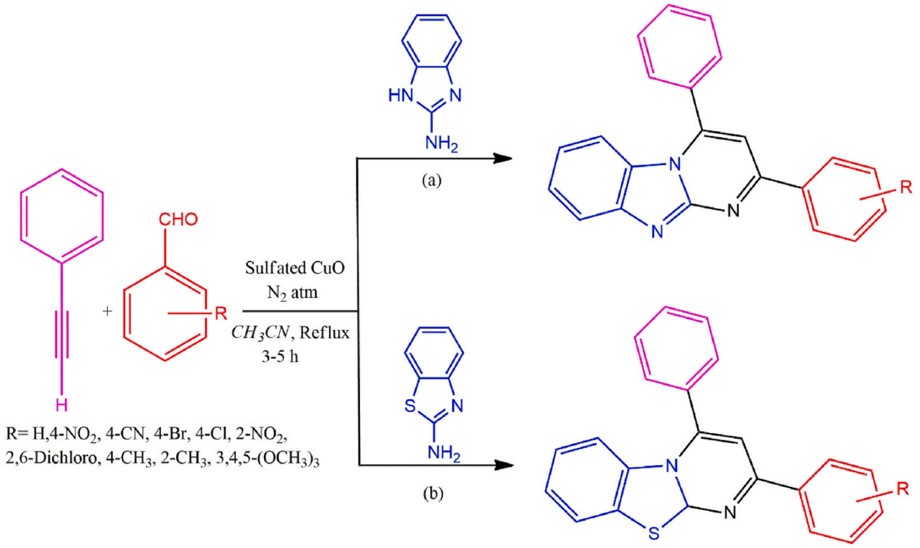
R = H, 4-Cl, 4-Br, 4-NO_2,4-OH, 4-CH_3, 4-OCH_3

Scheme 3. Nano SZ catalyzed synthesis of benzimidazoles derivatives [73].



X = O, S; R = H, 4-Cl, 4-Br, 4-NO_2,4-OH,
4-CH_3, 4-OCH_3

Scheme 4. Sulfated zirconia catalyzed synthesis of benzoxazoles/benzothiazoles derivatives [73].



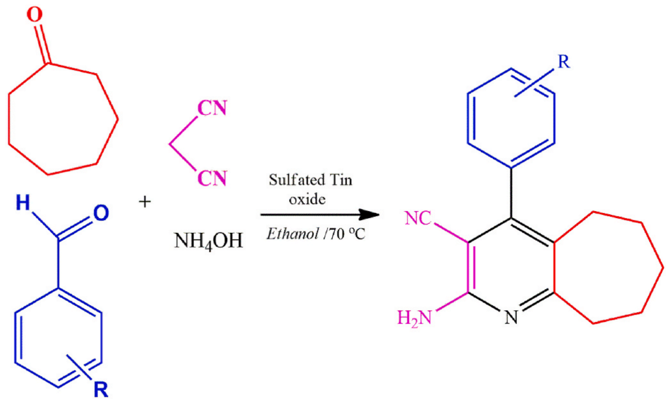
R= H,4-NO_2, 4-CN, 4-Br, 4-Cl, 2-NO_2,
2,6-Dichloro, 4-CH_3, 2-CH_3, 3,4,5-$(OCH_3)_3$

Scheme 5. (a) Synthesis of N-fused benzimidazolo pyrimidine using sulfated copper oxide; (b) Synthesis of N-fused benzothiazolo pyrimidine using sulfated copper oxide [85].

mechanism for mentioned N-fused heterocycles suggests the formation of imines by reaction between aldehydes with 2-aminobenzimidazole/2-aminobenzothiazole. However, sulfated CuO helped in further cyclization and dehydrogenation by activating phenylacetylene (alkyne).

3.5. Synthesis of pyridines

Pyridine derivatives not only find applications in pharmaceutical products but also in the production of chiral ligands and materials with photo- and electrochemical applications [86,87]. Selected bioactive C_2-functional pyridine derivatives are of importance to pharmaceutical industries [88]. Moreover, naturally occurring compounds such as vitamin B, nicotinic acid, and nicotinamide have pyridine as a part of structural skeleton responsible for their mode of action [89]. Pyridine derivative i.e., 2-Amino-3-cyanopyridine reported to have significant property as a potent inhibitor of HIV-1 integrase [90] and can be synthesized by multicomponent reaction between aldehyde, malononitrile, ketones, and ammonium hydroxide. It's typical synthesis over sulfated tin oxide was reported Koduri et al. at 70 °C [91]. For the synthesis, polar protic solvents showed better results over others (Scheme 6). 98 % yield of 2-Amino-3-cyanopyridine derivative was recorded for the reaction between benzaldehyde, NH_4OH, cycloheptanone, and malononitrile over 20 mg of sulfated SnO_2. However, in water only 25 % yield of product was obtained. Under identical reaction conditions, sulfated SnO_2 recorded excellent catalytic activity compared to SnO_2 and *p*-tolunesulfonic acid (PTSA). The major concern for the reported catalytic system is the deactivation of a catalyst. The catalyst was regenerated by calcination at 400°C–500 °C for 1 h. The mechanism involves the formation of arylidenemalononitrile intermediate as a Knoevenagel product of malononitrile and aromatic aldehyde. Arylidenemalononitrile later undergoes Michael addition with the ketone to give Michael adduct. Finally, condensation (intramolecular cyclization



R = H, 4-OCH_3, 2-Br, 4-Br, 2-Cl, 4-$N(CH_3)_2$, 2-OCH_3

Scheme 6. Four-component reaction for the synthesis of 2-amino-3-cyano-pyridines over sulfated Tin Oxide [91].

and air oxidation) of NH_4OH and Michael adduct results into pyridine derivative.

3.6. *Synthesis of 1,4-dihydropyridines*

Dihhydropyrimidine and its derivatives are analogous to NADH co-enzymes and can potentially participate in hydrogen transfer processes [92]. For example 1,4-dihydropyridines (1,4-DHPs) are known for their neuroprotectant and platelet *anti*-aggregatory activities along with several other biological properties and applications in the treatment of Alzheimer's disease, among others. 4-aryl-1,4-dihydropyridines in its dimeric form, serve as a nonpeptide HIV-1 protease inhibitor as well as a chemosensitizer to treat cardio-vascular disorders (tumour therapy) [93–96].

Synthesis of 1,4-dihydropyridine was reported in 1881 by Arthur Rudolf Hantzsch [97] where multicomponent reaction between aldehyde, two equivalents (eq.) of a β-keto ester, and ammonium acetate/ammonia as a nitrogen source was carried out. It is the most common reaction for the syntheses of symmetrical 1,4-DHPs [98]. Four-component reaction between amine, α, β-unsaturated aldehyde, β-keto ester, and alcohol yields 1,4-dihydropyridines. It was reported over different metal oxides and surface modified mixed metal oxides. Sulfated ceria-zirconia (20 wt% loading) recorded highest activity for the mentioned reaction (Scheme 7) [99].

Potentiometric titrations using *n*-butylamine were used to measure the strength (E_i) and the number of acid sites (mmolg^{-1}). Among different combinations of Ce:Zr ratios, sulfated $Ce_{0.07}Zr_{0.93}O_2$, exhibited highest acidity and thereby catalytic activity. The protocol showed substrate compatibility with 72–94 % yields of 1,4-dihydropyridine derivatives in acetonitrile at r.t. (Scheme 7) [99].

Koduri et al. successfully explored sulfated SnO_2, for the synthesis of 1,4-dihydropyridines. However, in reported protocol aldehyde, acetoacetanilide, and ammonium hydroxide were condensed in ACN at 80 °C [100]. When the reaction was carried out without catalyst under in water at 80 °C, 25 % yield of corresponding 1,4-dihydropyridine was obtained. No product formation was seen at r.t. The maximum yield was recorded for ACN compared to other solvents (Scheme 8) with reusability for five turns [100].

Another protocol includes syntheses of 1,4-dihydropyridines from aromatic aldehydes, β-dicarbonyls, and ammonium acetate. In reported protocol, various solid acid catalysts such as nanostructured sulfated zirconia, ZnO, γ-alumina, and ZSM-5 zeolites were screened for the mentioned synthesis at r.t. in ethanol [101]. Nanostructured SZ again recorded highest catalytic activity (80–94 % yield) due to highest acidity. Surprisingly, in polar protic solvent (EtOH) catalyst showed reusability for three cycles. Overall, in most of the cases acetonitrile was found as a best choice from the solvents for the syntheses of 1, 4-dihydropyridines.

3.7. *Synthesis of pyrazoles*

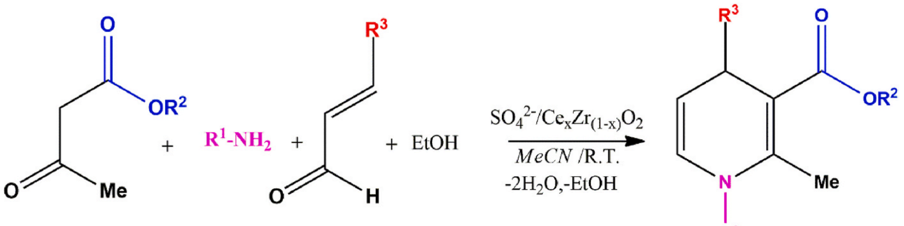
Pyrazole heterocycle is the part of various pharmaceutically commercially important drugs like Celecoxib, Sildenafil (Viagra), etc (Fig. 3). Celecoxib is used to treat arthritis, acute and menstrual pain [102]. Sildenafil is useful in treating erectile dysfunction in males [103]. Pyrazoles have received medicinal importance due to their antidiabetic [104], antimalarial [105], and antidepressant properties [106].

There are considerable attempts for their syntheses using solid acid catalysts [107–111]. Typically, pyrazoles are prepared by the one pot synthesis between hydrazines/hydrazides with 1,3-dicarbonyls. Various nanostructured ZnO, sulfated zirconia, γ-alumina, and ZSM-5 zeolites were evaluated as catalysts for synthesis of pyrazoles at r.t. in ethanol (Scheme 9) [112]. The order of catalytic activity observed is as follows.

Nano sulfated zirconia > nano -γ-alumina > nano ZnO > nano -ZMS-5.

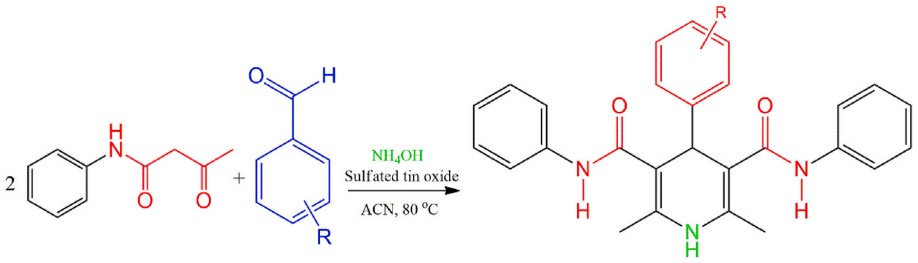
Alike in other studies, highest catalytic activity was recorded for nano SZ, prepared using sol-gel method, sulfated using concentrated H_2SO_4 followed by calcination (600 °C/2h).

An ultrasound-assisted synthesis of dihydropyrano [2,3-c]pyrazole derivatives was reported over nanostructured titania sulfuric acid (nano sulfated titania) catalyst [113]. The reaction between 3-methyl-1-phenylpyrazolin-5-one, aromatic aldehyde, and malononitrile was carried out over 15 nm sized mentioned catalyst in ethanol to achieve excellent yields (85–97 %) (Scheme 10). Different nano sulfated titania materials were prepared with change in concentration of chlorosulfonic acid during sulfation. Chlorosulfonic with loading of 5.0 mmol [H^+] per gram of the catalyst provided 91 % yield of the product in ethanol in 2.0 h under thermal heating. The reaction reached to completion in merely 15 min under ultrasound at 40 °C. Non sulfated catalyst under thermal conditions provided 43 % yield of the product. In reusability studies, after third run, decrease in acidity was observed from 5.0 mmol to 4.8 [H^+] per gram of catalyst [113].



R^1 = methyl, buytl, allyl, hexyl, heptyl, benzyl, Cl-benzyl
R^2 = OEt, OMe, R^3 = Ph, H, Me

Scheme 7. $SO_4^{2-}/Ce_xZr_{1-x}O_2$ catalyzed synthesis of 5,6-unsubstituted 1,4-dihydropyridines [99].



Scheme 8. SO_4^{2-}/SnO_2 catalyzed synthesis of 1,4-dihydropyridines [100].

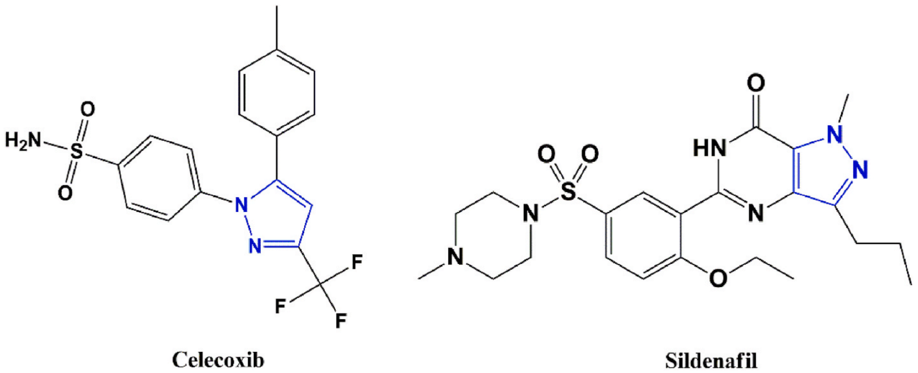
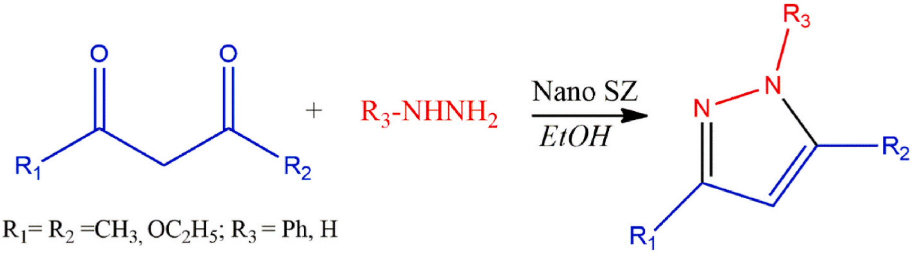


Fig. 3. Structure of Celecoxib and Sildenafil depicting pyrazole as a part of structure.



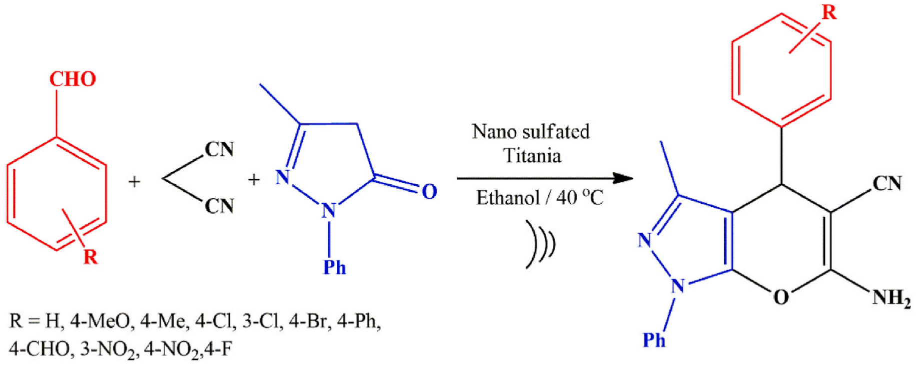
$R_1 = R_2 = CH_3, OC_2H_5; R_3 = Ph, H$

Scheme 9. Synthesis of Pyrazoles catalyzed by nano SZ.

3.8. Synthesis of pyrroles

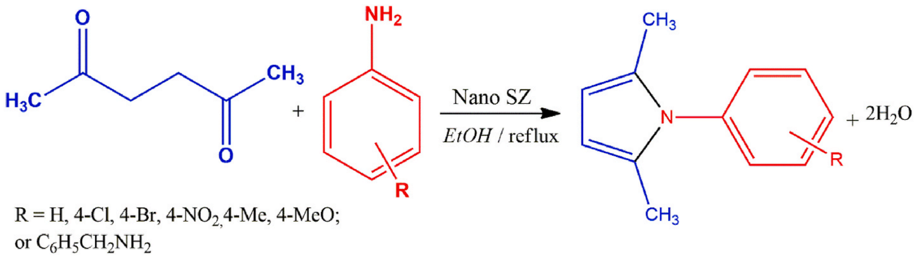
Five membered heterocycles like furan, thiophene, and pyrrole are synthesized by well-known Paal Knorr synthesis [114–116]. Among all, pyrrole is known to have a core unit in most of the medicinally important compounds [117]. Paal Knorr related synthesis of N-substituted pyrroles could be easily assessed over nano SZ at ambient temperature in ethanol (Scheme 11) [118]. Higher yields of products were achieved when the 2,5-diketone and primary amine were condensed in ethanol under reflux condition over nano SZ. A typical proposed mechanism, include the activation of carbonyl groups from 2,5-hexandione (2, 5-diketone) by acidic sites of catalyst, enhancing electrophilicity of carbonyl carbon followed by nucleophilic attack of amines. In mentioned work, author reported reusability of a catalyst for three consecutive cycles without loss in the activity [118].

Other than Paal Knorr, M. Hosseini-Sarvari et al., reported synthesis of pyrrole using Clauson-Kaas condensation approach [119]. Wherein, amines/diamines were successfully condensed with 2,5-



R = H, 4-MeO, 4-Me, 4-Cl, 3-Cl, 4-Br, 4-Ph, 4-CHO, $3\text{-}NO_2$, $4\text{-}NO_2$,4-F

Scheme 10. Synthesis of dihydropyrano [2,3-c]pyrazoles over nanostructured sulfated titania [113].



Scheme 11. Synthesis of pyrroles using nanocrystalline SZ [118].

dimethoxytetrahydrofuran over nanostructured sulfated titania (Scheme 12). Various screened polar protic and aprotic solvents such as DMF, DMSO, ethanol, and water provided moderate yields. Highest yield (98 %) was recorded under solvent free condition at 120 °C for the model reaction (Reaction between aniline and 2,5- dimethoxytetrahydrofuran). The protocol showed good substrate compatibility (80–98 % yield) with reusability of catalyst for three turns [119].

3.9. Synthesis of other heterocycles

Synthesis of few anticancer drugs have tertrahydroindoles as one of the important intermediates [120] which are conventionally prepared by cyclization of 1,4-dicarbonyls with a primary amine in presence of the dehydrating agent [121,122]. This conversion (Scheme 13) is well reported over SZ catalyst in toluene under reflux condition with considerable yield (80 %) of products. Surprisingly, in case of this reported protocol, decrease in the product yields (50–65 %) were recorded when substituted (-Br, –I, –NO_2, –CH_3, –OCH_3, etc.) anilines were used as primary amine source compared to unsubstituted aniline [123].

Quinoline is one of the important class of heterocycles having large number of applications in medicinal/pharmaceutical field such as NK-3 receptors [124], analgesic [125], antimalarial [126], antitumor [127], antiplatelet [128], among others [129–131]. Friedländer synthesis is one of the oldest routes for their synthesis by condensing 2-aminobenzaldehydes with ketones [132,133]. However, catalytic routes reported have notable drawback of either non-recoverable catalyst or laborious recovery. Friedländer synthesis of quinoline using 2-aminobenzophenone and ethyl acetoacetate (Scheme 14) is reported over montmorrilonite K-10, zeolite, and nano SZ in ethanol reflux condition. Nano SZ provided maximum yield with reusability wherein, filtered catalysts were first washed with acetone and then doubly distilled water followed by drying at 110 °C [134].

Coumarin class derivatives too have lot of medicinal applications such as inhibition of acetylcholinesterase, aromatase (breast cancer therapy) and squalene-hopene cyclase (cholesterol-lowering and anti-trypanosomal drugs) activity, *anti*-HIV, among others [130,135–137]. Typically, 4-hydroxycoumarin is known for the protection of liver cells from peroxides [137]. Considerable to excellent yields of coumarins from phenols and alkylacetoacetate (Scheme 15) were obtained over SZ under solvent free or in ethanol (80 °C). However, moderate temperature (65 °C) was employed for the reaction between ethyl 2-/4-chloroacetoacetate with 1,3 dihydroxy benzene to avoid formation of resin type material [138]. The synthesis was also reported over sulfated mixed metal oxides of ceria and zirconia under solvent-free conditions [139]. Introduction of Zr^{4+} ions into ceria unit cell and vice-versa tend to alter the surface properties, forming new Lewis and Brønsted, acidic and basic sites responsible for improved catalytic performance. In certain cases, formation of stronger acidic sites was observed after incorporation of metal ions [140,141]. However, the substrate scope was further extended when ethyl acetoacetate was condensed with di- and tri-hydroxybenzenes.

Mesoporous, tetragonal phase zirconia prepared by combustion method also showed significant yield of 7-hydroxy 4-methyl coumarin in autoclave at 150 °C at 1200 rpm [142]. Moreover, high sulfur concentration of 15.14 % (wt/wt) achieved after sulfation using chlorosulfonic acid, sulfuric acid, and ammonium sulfate helped in retaining the tetragonal phase. The absence of band at 1400 cm^{-1} in FTIR analysis is indicative of absence of polynuclear sulfate species on the catalyst surface. The kinetic studies revealed that the reaction is not influenced by external mass transfer and intraparticle diffusion resistance. However, the overall order of the reaction was found to be second-order with 36.0 $kJmol^{-1}$ of apparent activation energy [142]. Synthesis of coumarins is also reported under microwave over sol-gel derived nanosized SZ [143].

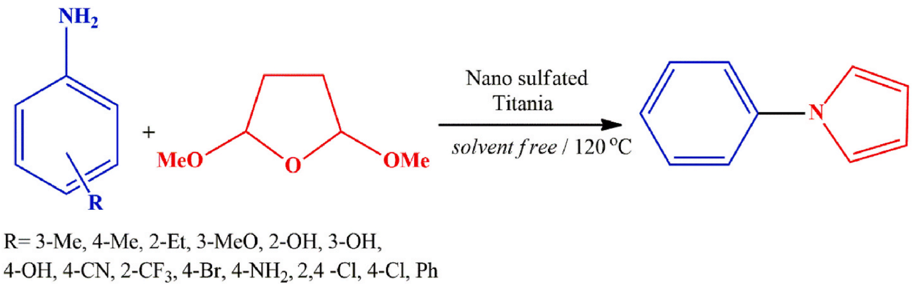
1,8-dioxo-octahydroxanthenes and 1,8 dioxo-decahydroacridines are the classes of heterocycles with various pharmaceutical applications reported over variety of catalyst materials [43]. For the same, the acidity of the sulfated oxide catalysts is used effectively for the synthesis of 1,8-dioxo-octahydroxanthenes (Scheme 16 a) and 1,8 dioxo-decahydroacridines (Scheme 16 b) in ethanol at 70 °C [144]. For the synthesis of xanthene by reacting benzaldehyde with 5, 5-dimethyl-1,3-cyclohexanedione, comparison of catalytic activities of various catalysts is as follows.

$$SO_4^{2-}/ZrO_2 > SO_4^{2-}/TiO_2 > SO_4^{2-}/SnO_2 > SO_4^{2-}/Fe_2O_3 > B_2O_3/ZrO_2 > PO_4^{3-}/ZrO_2 > SO_4^{2-}/CeO_2.$$

The highest activity of SZ is attributed to the presence of higher total number of acidic sites (*E*i value, 168 mV) compared to others. 1,8-dioxo-octahydroacridines could also be obtained by employing amine as additional reactant under identical conditions.

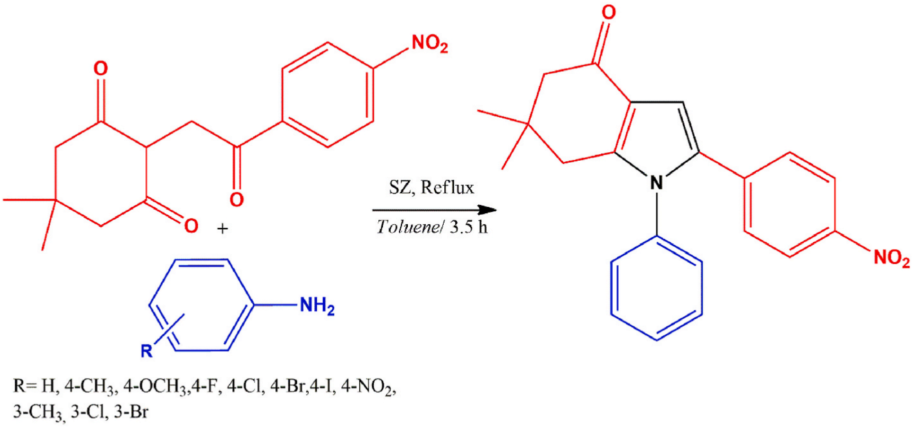
Cobalt-incorporated sulfated ($ZrO_2/SO_4^{2-}/Co$) nanocatalyst reported excellent catalytic activity for the synthesis of 1,8-dioxo-octahydroxanthenes in an aqueous media [145]. Incorporation of Co was confirmed by Co–O stretching vibration at around 566 cm^{-1} in FTIR analysis and also further confirmed by XRD. Crystallite size measured to be 12.0 nm using Scherrer's equation. A typical reaction mechanism over $ZrO_2/SO_4^{2-}/Co$ involving the role of Lewis and Brønsted acid site is well depicted below (Fig. 4) [145]. Sulfate ion grafted on iron stabilized ZrO_2 NPs ($SO_4^{2-}/_{(x\,=\,2\text{-}50)}$Fe–Zr–O) exhibited excellent catalytic activity for the synthesis of xanthenediones under microwave [146].

While screening different catalyst compositions (2–50 mol% of iron oxide), best results were recorded against the SO_4^{2-}/10Fe–Zr–O for the reaction between dimedone and 4-nitrobenzaldehyde with the reaction rate of 48 (mmol $h^{-1}g^{-1}$) and 90 % yield within 12 min. And the highest activity was attributed to highest SA (84 m^2/g), sulfur content (3.0 wt%) and acidity (0.60 $mmolg^{-1}$) [146]. This enhancement in activity is also recorded by the inclusion of metals (M = Fe, Cu, Co, Al, Cr and Mo) into

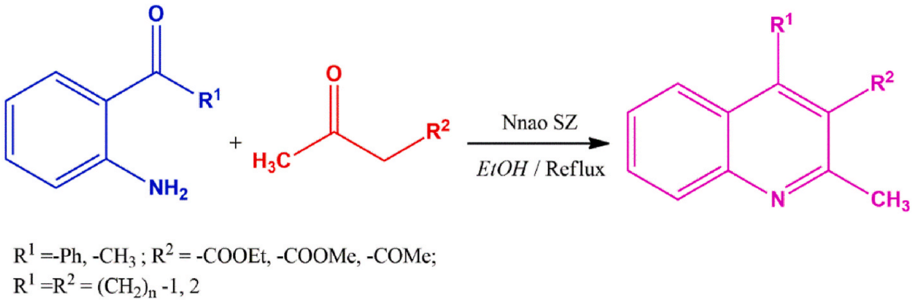


Scheme 12. Synthesis of pyrroles using nano sulfated titania [119].

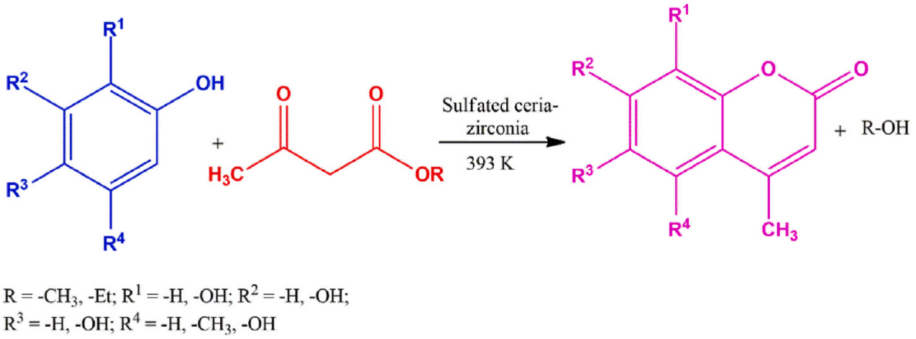
ZrO_2 [147]. Formation of oxygen (anionic) vacancies in zirconia by dopant like Fe^{3+} reported to stabilize the tetragonal phase of zirconia [148,149]. Spiroheterocyclic frameworks are found in various natural and synthesized molecules with important therapeutic actions [150]. Tailor er al., explored a benign domino protocol for synthesis of structurally diverse spiroheterocycles spiroannulated with 1,3,4-thiadiazolo [3,2-a] pyrimidine [151]. In mentioned work, reactants namely 2-amino-1,3,4-thiadiazole, isatin/N-methyl-4-piperidone/1,2-acenaphthylenedione, and carbonyl compounds were grinded together over various metal oxides (NiO, ZrO_2, ZrO_2/SO_4^{2-}, Fe_3O_4) NPs,



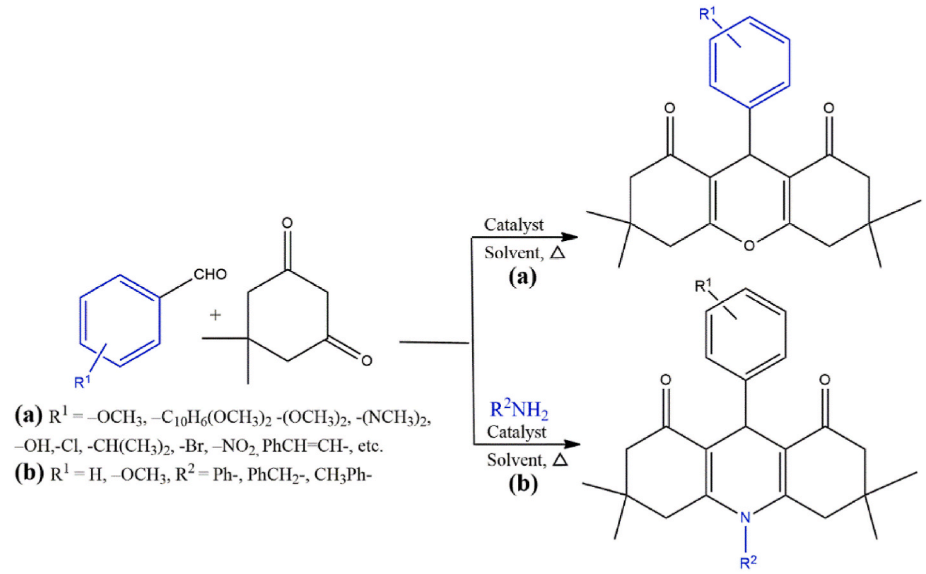
Scheme 13. Synthesis of Tetrahydroindolone using SZ catalyst [123].



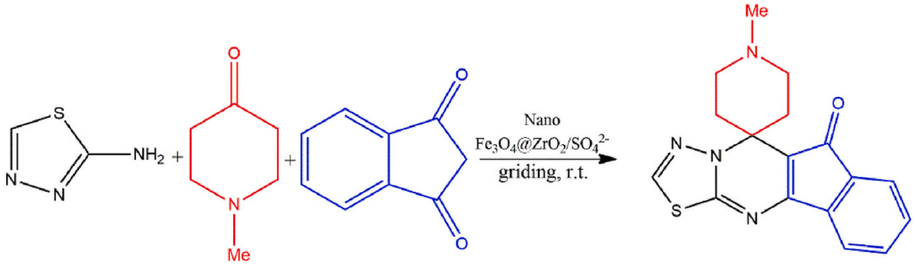
Scheme 14. Sulfated zirconia catalyzed synthesis of quinoline synthesis [134].



Scheme 15. Synthesis coumarins over sulfated ceria zirconia catalyst [139].



Scheme 16. Synthesis of 1,8-dioxo-octahydroxanthenes (Scheme 16 a) and 1,8 dioxo-decahydroacridines (Scheme 16 b) over sulfated oxides [144].



Scheme 17. Synthesis of 1,3,4-Thiadiazolo [3,2-a]pyrimidine catalyzed by $Fe_3O_4@ZrO_2/SO_4^{2-}$ [151].

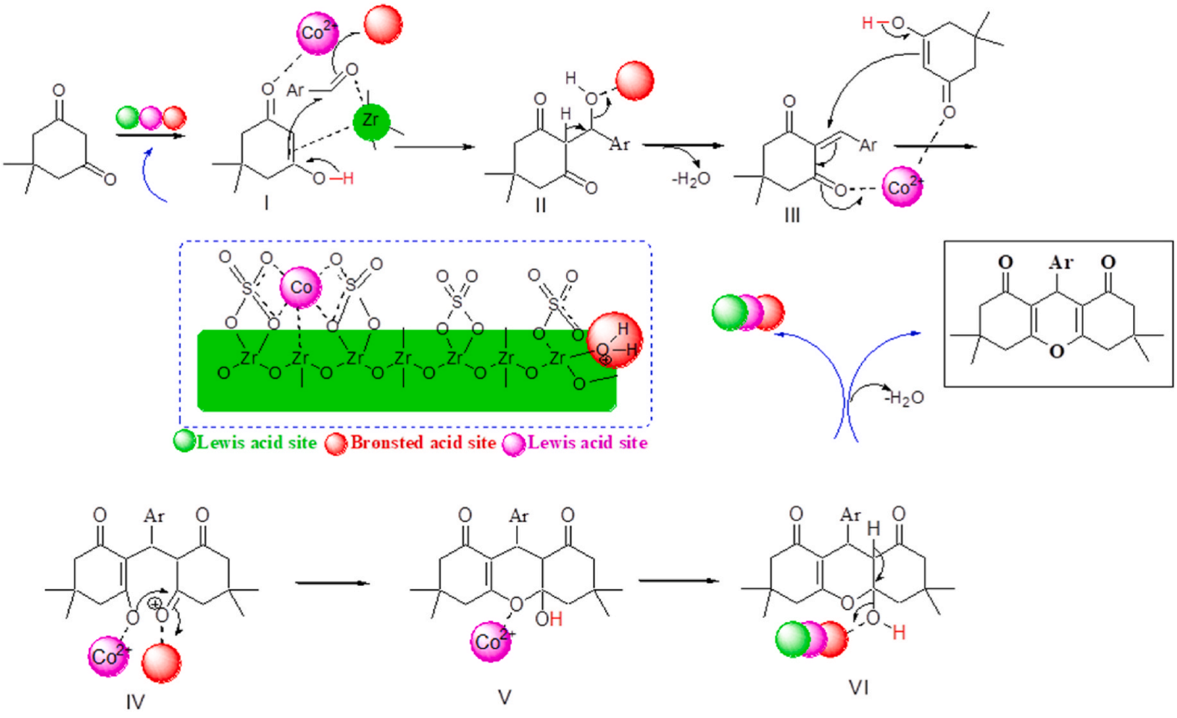


Fig. 4. Reaction mechanism for the synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by $ZrO_2/SO_4^{2-}/Co$ [145].

metal chlorides ($FeCl_3$ and $InCl_3$) and nano $Fe_3O_4@ZrO_2/SO_4^{2-}$ as a part of screening studies (Scheme 17). Among all, nano $Fe_3O_4@ZrO_2/SO_4^{2-}$ exhibited superior activity due to modification of acidic sites by Fe_3O_4 and also making catalyst magnetically retrievable. However, ionic nature of S]O, helped in generating Brønsted acidic sites improving further acidity and strength of a catalyst [151]. Sulfated catalysts are further explored for other heterocycles such as flavanones [152], and 1, 3-dioxane derivatives [153].

4. Leaching studies and scope

Sulfated zirconia and alumina reported to have excellent activities for the biodiesel production and thus tested for leaching studies. However, sulfated oxides found unsuitable for the industrial applications due to significant amount of leaching of SO_4^{2-} species [154]. The leaching of sulfate tends to decrease the catalytic activity after each run [155]. Interestingly, very less attention has been paid to protocols involving sulfated oxide catalysts for organic transformations. The leaching in aqueous medium, in particular at low pH was found predominant due to hydrophilic nature of acidic sites as well as hydrolysis of sulfate group [156,157]. In one of the cases of esterification over SZ, authors observed negligible or zero leaching of sulfate species under controlled conditions, attributed to coverage of acidic sites by hydrophobic reactants further preventing hydrolysis of sulfate species. The leaching issues in certain cases could also be prevented by working >100 °C i.e., boiling point above water, limiting the final conversion and or using one of the reactants in excess amount [158].

In last few decades large no of patents have been sanctioned displaying applications of sulfated oxides as catalysts. Selected patents are enlisted in Table 2 including various catalytic applications (isomerization, denitration, etc.) of sulfated oxides of Zr, Ti, Fe, Ce, etc. It proves the potential of sulfated oxides as catalyst materials. Though the acidity of sulfated oxides is very well utilized for various organic transformations as discussed in present manuscript, it is least explored for industrially for organic transformation. It surely represents the scope of the material, wherein the development of robust and novel catalyst material with desired activity along with arrested leaching will be helpful.

5. Conclusion and future prospects

Owing to the activities of sulfated oxides, in last few decades lot of attention has been paid to organic conversion over sulfated MOs/MMOs as catalysts. The sulfur content also helped in retaining the active tetragonal phase of zirconia. Various models have been proposed by authors over the decades for SZ. Among all, the models proposed by Arata, Ward et al., Rabee al, Clearfield et al., etc. showed Brønsted acidic sites in SZ. However, superacidity of SZ is highly debatable. In other studies, highest acidic strength was recorded $H_o \leq -16.4$ with lesser SA compared to other methods.

In vapor phase protocols, the deactivation of the catalysts was observed due to the decomposition of sulfate species to sulfur oxides and H_2S. However, in liquid phase particularly, in aqueous media leaching of the sulfate group is the major concern. Decline in catalytic activity was quite evident from the data that after few runs, in reusability studies. Leaching of sulfate species decreases the catalytic activity due to the loss of acidic sites. Leaching is more prominent in an aqueous media and at lower pH. Interestingly, most of the authors restricted the reusability studies for three or five turns.

In nutshell, sulfated catalysts and mostly SZ showed excellent catalytic activities for the synthesis of pharmaceutically important heterocycles. However, more studies with respect to leaching for a greater number of turns, scalability, and detailed mechanistic investigations are still lacking. SZ and other sulfated oxides undoubtedly are excellent solid acid catalysts, however, further careful investigations in identifying the role of material, detailed study of active sites, deactivation

Table 2
List of selected patents on sulfated oxides and their catalytic applications.

Sr. No.	Catalyst and Sulphating agent	Reaction studied and conditions	Yield/Conversion/Selectivity (Important outcomes)		Patent number and Year of grant	Reference
1	$CuO/SO_4^{2-}/ZrO_2$ [H_2SO_4]	Catalytic activation method of alkali lignin in black liquor (Temp: 100 °C, Time- 4h)	Name of the content Total hydroxyl Phenolic hydroxyl group Alcoholic hydroxyl group	Content increased by 93.85 % 26.74 % 155.41 %	CN103724632A (2016)	[159]
2	SO_4^{2-}/TiO_2 [H_2SO_4]	Preparation of selective di-styrenated phenol (40–140 °C, 1–6h) Inert atmosphere	At 140 °C, Conversion of phenol and styrene 99.99 %		KR101808042B1 (2017)	[160]
3	CeS/Al_2O_3, CeS/TiO_2, CeS/ZrO_2 (S - SO_4^{2-}) [$(NH_4)_2SO_4$]	Denitration catalyst applied to coal-fired flue gas Temp: 250–500 °C.	CeS/Al2O3 > CeS/TiO_2 > CeS/ZrO2		CN105457659B (2018)	[161]
4	Sulfated zirconium oxide and a binder aluminum oxide, promoter group II metal, Ca, platinum and/or palladium [$H_2SO_4/(NH_4)_2SO_4/H_2S$]	Isomerization of C4–C7 paraffins (Temp.100–200 °C)	Conversion 78-8- 86.6 %	Yield % 97.1–99.8 %	US10384196B2 (2019)	[162]
5	SO_4^{2-}/TiO_2, SO_4^{2-}/ZrO_2, SO_4^{2-}/Fe_2O_3 [$H_2SO_4/(NH_4)_2SO_4$]	Preparation methods of fire retardant phosphonic acids three (1,3- bis- chloropropyl) ester (Using phosphorus pentoxide and dichlorohydrin)	Catalyst SO_4^{2-}/TiO_2 SO_4^{2-}/ZrO_2 $SO_4^{2-}/ZrO_2–Fe_2O_3$ $SO_4^{2-}/TiO_2–Fe_2O_3$ $SO_4^{2-}/TiO_2–ZrO_2$ $SO_4^{2-}/TiO_2–ZrO_2–Fe_2O_3$	Yield (%) 85.8 85.3 84.5 86.3 85.7 87.8	CN109232639A (2021)	[163]
6	$SO_4{}^{2-}/ZrO_2$-MCM-41 with Zr-based solid ionic liquids [$Zr(SO)_4)_2$]	Preparation process of methyl ethyl ketone from 2, 3-butanediol temp.- 250 °C, 48 h	Conversion of 2, 3-butanediol 99.5 %	Selectivity of methyl ethyl ketone 98.2 %	CN113101970A (2022)	[164]

mechanisms in liquid phase, etc. will help in developing sustainable catalytic protocols.

Ethical approval

Not applicable.

Authors' contributions

All authors approved the final version of submitted manuscript. **SSK**: Conceptualization, writing an original draft, resources, and supervision. **TAF**: Visualization, editing, writing, resources, and coordination. **ASB**: Writing an original draft, review, and editing, formal analysis, and overall review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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