Sulfated tungstate: a new solid heterogeneous catalyst for amide synthesis†

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Amide formation avoiding poor atom economy reagents is a priority area. We have synthesized sulfated tungstate as a new reusable and environmentally benign heterogeneous catalyst for direct amide formation between carboxylic acid and amine. It has potential for large scale applications.

A recent report by the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) has found that amide formation avoiding poor atom economy reagents is the priority area of research for the pharmaceutical industry.[1] As many as 65% of drug molecules prepared by leading pharmaceutical companies contain an amide unit, indicating its importance and prevalence in synthetic organic chemistry.

Formation of amides usually involves a pyrolysis reaction between carboxylic acid and amine at a very high temperature (>180 °C); this is incompatible with most functionalised molecules.[2] Activation of carboxylic acids[3] by forming acid chlorides, anhydrides or esters requires a separate step and this protocol suffers from low atom economy. Various coupling reagents have been used to activate carboxylic acids including stoichiometric activators such as bis[bis(trimethylsilyl)amino] tin(II),[4a] titanium tetrachloride,[4b] trimethylaluminium,[4c] Lawesson's reagent,[4d] tetrazoles,[4e] benzoxazoles,[4f] oxalates,[4g] phosphonium reagents, carbodiimides and uronium salts,[4h] to effect amidation. The limitations of these reagents are stability, hazardous nature, toxicity, cost and the requirement of removal of by products that complicate the isolation of the desired amide. The other classes of amide condensation reactions are catalyzed by arylboronic acids[5] and boric acid[6] and they generally offer more attractive reaction conditions. The best result was obtained using *o*-iodophenylboronic acids at room temperature.[7] These are homogeneous catalysts and most of the homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1–20 mol%) and trace amounts of the catalyst must be recovered from the reaction products. This has hampered this methodology for large scale synthesis.

There have been new developments in the intervening years, including use of solid acid catalyst[8] and microwave assistance[9] for amidation. With current environmental concern, replacement of "non-green" reagents by "green" solid acid catalysts has great industrial relevance. We were seeking a heterogeneous solid acid catalyst for amidation and we succeeded. Herein, we report an efficient green process for amidation using sulfated tungstate as a solid acid catalyst. The catalyst is well characterized and the reaction conditions have also been standardized.

In FTIR characterization, a pattern of three featured peaks at 953 cm^{-1} (W=O), 885 cm^{-1} (W–O–W) and 657 cm^{-1} (W–O) indicate the presence of polytungstates in the catalyst. Bands for S=O stretching vibrations at 1230 cm^{-1} and 1098 cm^{-1} and an –OH stretching vibration at 3434 cm^{-1} confirm the presence of a sulfonic group. The absence of a band at 1400 cm^{-1} indicates that there is no formation of polynucleated sulfates $S_2O_7^{2-}$ on the surface of the catalyst. A band at 1626–1653 cm^{-1} is attributed to the O–H bending frequency of water molecules associated with the catalyst. Fig. 1 shows the XRD patterns of the catalyst. The appearance of halo peaks around 13°, 30° and 55° indicate an amorphous nature.

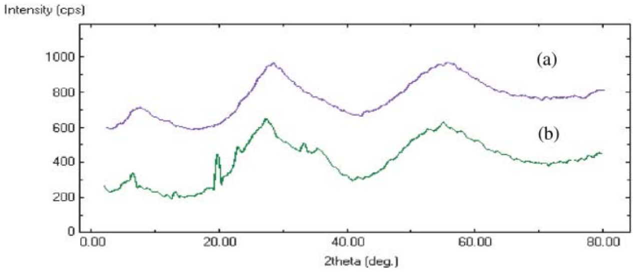

Fig. 1 XRD patterns of the catalyst (a) "fresh" catalyst (b) "recovered" catalyst after fourth use.

Thermogravimetric analysis is most frequently employed for dynamic study of heteropolyacid hydrate decomposition.

TGA-DSC analysis of the catalyst shown in Fig. 2 indicates a slow decrease in sample weight from ambient temperature.

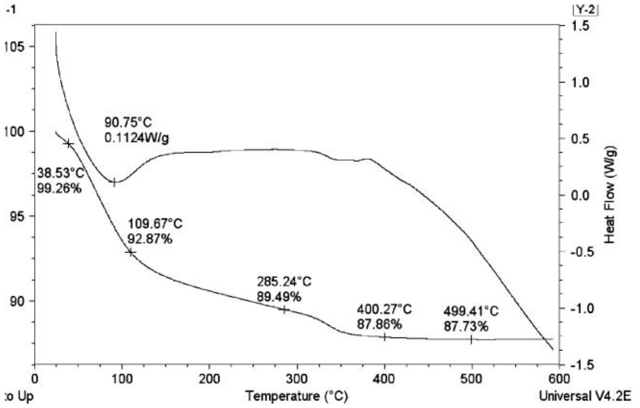

Fig. 2 TGA-DSC curve of sulfated tungstate.

The departure of loosely bonded water molecules hastens at 90–100 °C being endothermic at 91 °C and reaching completion

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Table 1 Physicochemical properties of catalyst

	Elemental analysis[a] (wt%)				EDAX[b] (wt%)					Acidity	
Entry	C	H	N	S	S	W	O	BET[c]surface area (m^2 g^{-1})	Particle size/μm	No. of acid sites in mmol g^{-1}	E_i/mV
Sulfated tungstate	0.00	0.80	0.00	0.30	0.31	69.13	30.55	1.90	1.49	0.65	373.00

[a] Elemental analysis (accuracy ± 0.1). [b] Energy-dispersive X-ray spectroscopy (accuracy ± 0.01). [c] Brunauer–Emmett–Teller surface area measurement.

at about 300 °C. The mass of the sample remains virtually constant on heating from 300 °C to 600 °C.

Table 1 presents the physicochemical properties of the catalyst. Elemental analysis showed complete absence of Cl^- species and the presence of 0.3% w/w sulfur as sulfate. Therefore such a low sulfur content in the catalyst confirms lower Brønsted acidity as compared to a heteropolyacid.[10] The elemental distribution mapping of the catalyst by EDAX shows a constant tungsten : oxygen : sulfur signal ratio of 69.13 : 30.55 : 0.31 wt% over different areas. The sulfur composition was in accordance with the sulfur content obtained by elemental analysis. The SEM images given in Fig. 3 show aggregates of particles and the amorphous nature of the catalyst.

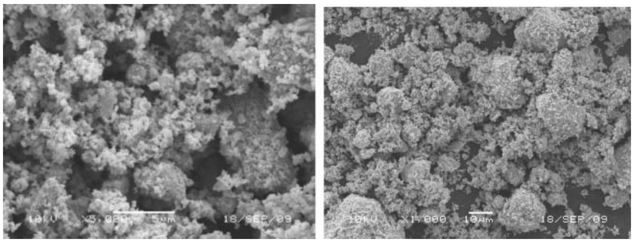


Fig. 3 Scanning electron microscope (SEM) image of sulfated tungstate.

Aggregation of fine particles of the catalyst after drying results in a lower surface area of the catalyst (1.9 m^2 g^{-1}). Analysis of the particle size of the catalyst by a particle size analyzer also supported the above hypothesis.

The total number of acidic sites and their relative strength was determined by potentiometric titration with *n*-butylamine. The catalyst (0.05 g) was suspended in 10 ml of acetonitrile and agitated for 3 h at room temperature. This mixture was titrated against 0.05 N *n*-butylamine in acetonitrile at a rate of 0.05 ml min^{-1}. In this method the initial electrode potential (E_i) indicates the maximum acidic strength of the catalyst and the end point of the titration expressed in mmol g^{-1} indicates the total number of acid sites.[11] Further, the acid strength of those sites may be classified according to the following scale, E_i > 100 mV (very strong sites), 0 mV < E_i < 100 mV (strong sites), −100 mV < E_i < 0 (weak sites) and E_i < −100 mV (very weak sites).

Fig. 4 shows the titration curves of some selected solid acid catalysts and sulfated tungstate. According to this scale, silica (60–120 mesh) shows strong sites[12] at E_i = 1 mV while tungstic acid and sulfated tungstate show very strong sites at 312 and 373 mV with a total number of acidic sites at 0.25, 0.5 and 0.65 mmol g^{-1} of catalyst respectively.

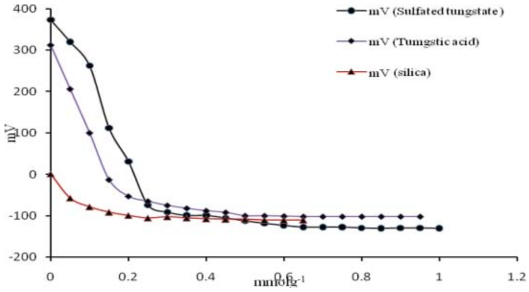
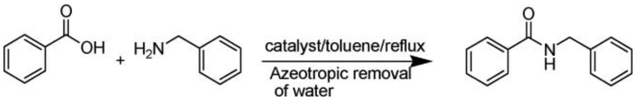


Fig. 4 Potentiometric titration curves for sulfated tungstate, tungstic acid and silica.

Heteropolyacids have a greater Brønsted acidity and show an initial potential value[13] in the range of 600–1100 mV.

Therefore, the Brønsted acidity of sulfated tungstate is expected to be somewhere between heteropolyacid and silica due to low sulfur (0.3 wt%) as sulfate present on the surface of the catalyst.

An amidation reaction between benzoic acid and benzylamine was selected as a model (Scheme 1). During the optimisation study, azeotropical removal of water was necessary to progress the reaction so the temperature factor was ignored.



Scheme 1 Amidation reaction between benzoic acid and benzylamine.

To understand the role of the catalyst we studied the effect of catalyst amount on the formation of amide. The results are depicted in Fig. 5.

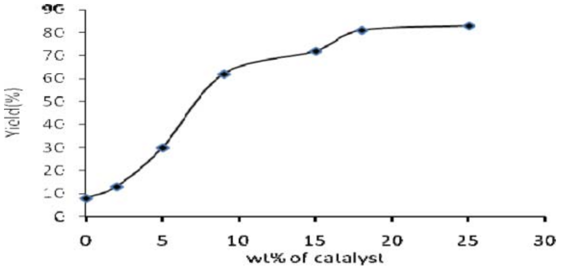


Fig. 5 Graph of isolated yield of *N*-benzylbenzamide *versus* wt% of the catalyst (reaction conditions: benzoic acid (2 g, 16.39 mmol), benzylamine (1.59 g, 14.9 mmol), and time 12 h).

Table 2 Effect of different acid catalysts for the formation of *N*-benzylbenzamide[a]

Entry	Catalyst	Yield[b] (%)
1	$H_3PW_{12}O_{40}$	04
2	*p*-Toluenesulfonic acid	10
3	Camphorsulfonic acid	12
4	Sulfated tungstate	81
5	Tungstic acid	20
6	Silica	24
7	Nil	08

[a] Reaction conditions: benzoic acid (2 g, 16.39 mmol), benzylamine (1.59 g, 14.9 mmol) and catalyst 18 wt% for 12 h azeotropical reflux in toluene. [b] Isolated yield.

Table 3 Catalyst reusability

	% Yield of *N*-benzylbenzamide	
Run no.	Type A (with makeup)[a]	Type B (without make up)
Fresh	81	81
First recycle	82.5	79
Second recycle	81	78
Third recycle	80	76
Fourth recycle	81	75

[a] Loss of catalyst (<5%) during handling was made up by fresh catalyst.

The catalyst amount was varied over a range of 2–25 wt% of total mass of the reactants. The profile of the curve indicates that the rate of reaction is directly proportional to the amount of the catalyst and reaches a plateau at about 18 wt%. Further studies were performed with 18 wt% of catalyst. The mole ratio of acid to amine was varied from 4 : 1 to 1 : 3 under the same set of reaction conditions. No significant increase in yield was observed beyond a mole ratio of 1.1 : 1 of acid/amine.

To assess the standing of the catalyst among other acid catalysts, comparative experiments were performed and the results are given in Table 2. The yields obtained using sulfated tungstate as a catalyst are very high compared to heteropolyacid and silica. This observation is consistent with expectations of its acidity being between heteropolyacid and silica.

It is noteworthy that the catalyst was recovered simply by filtration without any acidic or basic workup even after its fourth use. Two types of experiments were performed and the results are given in Table 3. The results indicate that the catalyst was stable and reusable four times without any loss of activity.

The XRD pattern of the catalyst recovered after its fourth use is shown in Fig. 1. A similarity in the patterns indicates that the structure of the catalyst was unchanged.

In order to prove that the reaction is heterogeneous, a standard leaching experiment was conducted. The catalyst was filtered at the reaction temperature and the reaction was allowed to proceed without a catalyst. There was no change in yield even after 12 h reflux, indicating that no homogeneous catalyst was involved.

To explore the generality and scope of the catalyst for amide synthesis, the reaction was examined with structurally diverse carboxylic acids and primary and secondary amines as shown in Table 4. Reactions were also carried out in the absence of catalyst to ascertain the role of the catalyst. In all cases, the reaction proceeded cleanly and desired amides were obtained in high yields.

Aromatic substrates, benzoic acid and aniline also reacted well under the reaction conditions with 18 wt% of catalyst giving 45% yield of benzanilide in 14 h (entry 2, Table 4). The same reaction reported by Clark *et al.* using K60 silica[8] as a catalyst required 50 wt% of catalyst for 24 h reflux in toluene to give a similar yield and this establishes the superiority of sulfated tungstate. Ibuprofen amides have been reported to display improved anti-inflammatory activity and less toxicity.[14] Amidation of ibuprofen as well as lauric acid with benzylamine led to the corresponding amides in very good yields with 12 wt% of the catalyst (entries 8 and 12, Table 4). No side reaction was observed with substrates having an unprotected hydroxyl group and double bond in the carboxylic acids during the course of reaction (entries 9–11, Table 4). In some cases the use of xylene was necessary in order to provide higher yields (entries 7 and 9, Table 4).

To measure the "green-ness" of the reaction, we used different parameters of green chemistry. Table 5 shows a comparison of the catalyst with different activators.

It is noticed that sulfated tungstate is considerably cleaner and more competent than other activators. In particular, the waste produced (*E*-factor) during the reaction was much less compared to IBA and that of conventional methods. However, the *E*-factor ignores recyclable factors such as recycled solvents and reused catalyst, which obviously increases the accuracy.

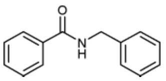
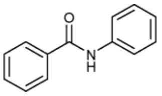
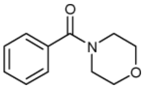
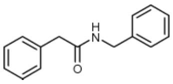
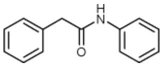
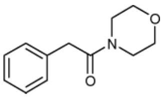
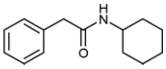
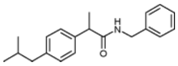
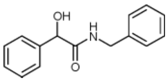
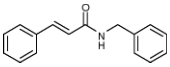
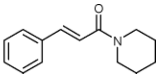
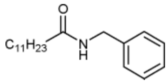
Experimental section

FTIR spectra were recorded on a Perkin Elmer IR Spectrophotometer with a KBr disc. Wide angle XRD patterns of the catalyst were obtained on a Rigaku miniflex X-ray Diffractometer with monochromatic Cu-Kα radiation (λ = 0.154 nm) operated under 30 Kv and 15 mA. The 2θ value was scanned in the range of 2°–80° with a resolution of 2 min^{-1} at 21 °C. TGA-DSC analysis was performed on TA Q600 series with heating rate 10 °C min^{-1} up to 600 °C under nitrogen atmosphere. The sulfur content was determined by a CHNS analyzer using Thermo Finnigan Flash EA 1112 series equipment. The specific surface area of the catalyst was determined by nitrogen adsorption/desorption technique using Micromeritics Accusorb 2020 equipment. Surface area was calculated using the BET equation. The particle size analysis was measured on a Malvern Nano-ZS Zetasizer instrument. Scanning Electron Microscope coupled with an Energy Dispersive X-ray Micro analyzers (EDAX) were obtained on Jeol JSM 638DLA equipment. Acidity of the catalyst was measured by means of potentiometric titration. The electrode potential variation was measured with an instrument R. I. digital pHmeter, using a double junction electrode.

Conclusions

In conclusion, we have prepared sulfated tungstate as a stable, cost-effective and reusable solid inorganic acid catalyst useful for

Table 4 Isolated yields for direct amide formation[a]

Entry	Solvent	Catalyst (wt%)	Time/h	Product	Yield (%)
1	Toluene	0 9 18	24[b] 12 12		8 62 81
2	Toluene	0 9 18	24 16 14		8 32 45
3	Toluene	0 18	24 24		0 33
4	Toluene	0 8 15	24 14 12		24 83 96
5	Toluene	0 9 18	24 18 18		18 56 72
6	Toluene	0 9 18	24 12 12		15 45 72
7	Xylene	0 8 12	24 18 16		23 81 98
8	Toluene	0 12	24 12		18 98
9	Xylene	0 12 16	24 18 18		22 78 86
10	Toluene	0 8 15	24 16 14		23 78 95
11	Toluene	0 8 16	24 12 12		19 52 72
12	Toluene	0 7 12	24 18 12		26 84 96

[a] Conditions: acid (1.1 equiv), amine (1.0 equiv) and catalyst (appropriate amount) reflux in a solvent with azeotropic removal of water. [b] No significant increase in yield was observed after 12 h up to 24 h.

amidation between carboxylic acid and amines. By measure of "green-ness" it appears to be a more promising green alternative over conventional methodologies for amide synthesis.

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Table 5 A comparison of "green-ness" between the catalyst/activators in the preparation of *N*-benzylbenzamide

Activators	*E*-factor[a]	Mass intensity	Atom economy (%)	Yield[b] (%)
IBA[c]	251.7	397.3	92.13	50
CDI[d]	31.8	32.9	53.9	92
DCC	22.6	67	48.5	82
$SOCl_2$	17	25	85.3	72
Sulfated tungstate	9.3	26.3	92.13	81

[a] *E*-factor shown does not account for the waste produced in the synthesis of activators. [b] Isolated yield of *N*-benzylbenzamide. [c] *ortho*-*N*,*N*-diisopropylbenzylaminoboronic acid catalyst. [d] *N*,*N*-carbonyldiimidazole.

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