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Sulfated tungstate: An efficient catalyst for synthesis of thioamides via Kindler reaction

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ABSTRACT

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Sulfur

New application of sulfated tungstate, a mildly acidic solid inorganic acid, as reusable heterogeneous catalyst for efficient Kindler reaction, a three component reactions of aldehydes, amines and sulfur, for synthesis of thioamides is discussed.

Keywords: Kindler reaction Thioamides Sulfated tungstate Heterogeneous catalysis Amines Aldehydes

1. Introduction

Appreciating the campaign for green chemistry and continuing pressure on limiting resources, chemical sustainability has become a focal point of research. One of the approaches toward chemical sustainability can be through development of catalytic methods with environmentally benign, easy to recover and reusable catalyst. Recently our group, working toward this goal, has synthesized and well characterized sulfated tungstate [1], as green, reusable, heterogeneous, mildly acidic catalyst and demonstrated its effectiveness in amide bond formation [1,2], Biginelli [3], Willgerodt-Kindler [4] and Strecker [5] reactions. On the same track it was thought that sulfated tungstate might catalyze Kindler reaction [6], a three component reaction of aldehyde, amine and sulfur satisfactorily conducted under acid catalyzed conditions, for synthesis of thioamides and indeed this was observed. Thioamides are an important class of compounds and show broad spectrum of bioactivity such as antibacterial, antimycobacterial, antiulcerative, fungicidal, anticancer and spasmolytic [7-13]. Ethionamide and prothionamide are two examples of thioamide containing drugs which are in clinical use for treatment tuberculosis. Thioamides find wide applications as intermediates in synthesis of five and

six membered heterocycles [14-17], and active pharmaceutical ingredients such as fentiazac, fenclosic acid and febuxostate [18,19]. A good number of preparative methods are available in literature for synthesis of thioamides and the most frequently used methods are based on thionation of amides. Thionation of amides is affected using thionating reagents, such as P_4S_{10} [20–25], diethylthiocarbamoyl chloride [26], ethylaluminum sulfide [27], boron sulfide [28,29], use of PSCl₃/H₂O/Et₃N system [30] and Lawesson's reagent [31]. Thionation of amides is also achieved by activation of amides with electrophilic reagents, such as oxalyl chloride and phosphorousoxychloride and benzyltriethylammonium tetrathiomolybdate [32] and hexamethyldisilathiane [33], followed by treatment with thionating agents. These approaches suffer from drawbacks like toxicity of reagents, bad odor, corrosive nature, explosive properties, formation of uncontrolled by-products with lower yields. In the past few years, improved reagents such as fluorous based Lawesson's reagents [34], encapsulated P₄S₁₀ [35] and polymer supported thionating agents [36] have been developed to address some of these drawbacks. Willgerodt-Kindler [37,38] and Kindler reactions [6], classical three component reactions of ketones/aldehydes, amines and sulfur, are direct oxidative sulfurization methods for thioamide synthesis. Kindler reaction, where the three components are aldehyde, primary/secondary amines, ammonia or ammonium salt and sulfur, has potential for wide applicability for synthesis of diverse set of useful thioamides in one pot with high atom economy and with water as the only condensation by-product, because a large



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Scheme 1. Kindler thioamidation reaction of benzaldehyde, aniline and sulfur.

Table 1Optimization of catalyst amount and solvent.^a

Entry	Solvent	Sulfated tungstate (wt%)	Temperature (°C)	Time (h)	Yield ^b (%)
1	DMF	-	110	24	15
2	DMF	1	110	12	34
3	DMF	5	110	12	69
4	DMF	10	110	8	90
5	DMF	20	110	8	91
6	DMF	10	rt	12	-
7	DMF	10	60	12	26
8	DMF	10	90	12	65
9	Neat	-	110	24	10
10	Neat	10	110	12	56
11	DMSO	10	130	12	79
12	NMP	10	150	12	60

^a Reaction condition: benzaldehyde (1 g, 9.4 mmol), aniline (1.1 g, 11.8 mmol) and sulfur (0.38 g, 11.8 mmol) at different temperature.

^b Isolated yield.

number of aldehydes and primary/secondary amines, ammonia and its salts are readily and commercially available. The classical Kindler reaction method has many drawbacks, however, some attempts have been made toward improvement by Oliver Kappe et al. by using microwave flash heating in *N*-methylpyrrolidone as solvent [39]. This modification, though does not show any potential for large scale application, has allowed preparation of wide range of thioamides in good yields. Another recent modification, developed by Kanbara and co-workers [40] using Na₂S·9H₂O, gave promising results; however, the method still suffered from drawbacks like long reaction time, requirement of relatively large amount of catalyst and removal of trace amounts of catalyst from reaction products. Having seen the present status of various methods for thioamide synthesis, with many drawbacks as indicated by literature, clearly show that there is a scope for newer and better methods. Therefore we got interested in investigating suitability of sulfated tungstate as heterogeneous catalyst for Kindler reaction and the results are presented here.

2. Experimental

2.1. Materials and methods

General: ¹H NMR of all the products were recorded at 300 MHz in CDCl₃ as solvent and chemical shift values are expressed in δ ppm

Table 2
Mole ratio study.

Entry	Benzaldehyde:aniline (mole ratio)	Sulfur (mole ratio)	Yield ^b (%)
1	1:1	1	76
2	1:1.25	1	80
3	1:1.25	1.25	90
4	1:1.50	1.50	92
5	1:1.50	2	92
6	1.25:1	1.25	74%

^a Reaction was performed with 1 g, 9.4 mmol of benzaldehyde and appropriate mmol of other reactants with 10 wt% of catalyst in DMF for 8 h at 110 $^{\circ}$ C. ^b Isolated yield.

 Table 3

 Effect of different acid catalysts for formation of N-phenylthiobenzamide.³

Entry	Acid catalyst	wt%	Time (h)	Yield ^b (%)
1	Nil	-	24	15
2	Acetic acid	20	12	40
3	p-Toluenesulfonic acid	20	12	64
4	Silica	20	12	34
5	Tungstic acid	20	12	17
6	Sulfated tungstate	10	8	90

 $^a\,$ Reaction conditions: benzaldehyde (1 g, 9.4 mmol), aniline (1.1 g, 11.8 mmol), and sulfur (0.38 g, 11.8 mmol) at 110 $^\circ C$ in DMF for 8 h.

^b Isolated yield.

relative to tetramethylsilane (Me₄Si) signal as internal reference. IR spectra were recorded as KBr pellet. All compounds were analyzed using the same HPLC conditions: isocratic elution (0.05% CF₃COOH, Water/CH₃CN 15:85), flow rate = 0.5 ml/min, T = 25 °C, UV detection at 260 nm with column Purosphere, RP-18e (5μ m). All the solvents were purchased from commercial sources and were used without further purification. Preparation and characterization details of sulfated tungstate are given in our previous work [1].

2.2. General procedure for sulfated tungstate mediated synthesis of thioamides

Sulfated tungstate (10% w/w) was added to a mixture of benzaldehyde (1 g, 9.43 mmol), aniline (1.1 g, 11.8 mmol) and sulfur (0.38 g, 11.8 mmol) in DMF (10 ml) and the suspension was stirred at 110 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with EtOAc (15 ml) and filtered to recover the catalyst. The organic layer was washed with saturated aq. NH₄Cl solution (20 ml), water (2 × 50 ml), dried over Na₂SO₄ and concentrated under reduced pressure to get crude product; which was purified by chromatography on silica gel with hexane–ethyl acetate (8:2) as eluent to get pure thiobenzanilide as pale yellow solid (Scheme 1), m.p. 97–98 °C (lit. [40] 99 °C); IR (KBr): 3328, 1497, 1445, 1208 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ =9.0 (br. s. 1H), 7.31–7.16 (m, 10H). ¹³C NMR (75 MHz, CDCl₃): δ =127.0, 127.5, 128.7, 129.1, 131.0, 135.7, 140.5, 189.2.

All the products were known compounds and were characterized by IR, ¹H NMR spectroscopic data, melting points and compared with reported values.

Table 4	
Reusability	study

Run no. ^b	% Yield of N-phenylthiobenzamide
Fresh	90
First recycle	89
Second recycle	88
Third recycle	86
Fourth recycle	86

^a Reaction condition: benzaldehyde (1 g, 9.4 mmol), aniline (1.1 g, 11.8 mmol) and sulfur (0.38 g, 11.8 mmol) at 110 $^{\circ}$ C for 8 h.

^b Loss of catalyst (<5%) during handling.

Table 5 Substrate scope. ^a					
0 R ₁ + S ₈	+ HN R_2 $tu $ R_3 DMF	$ \begin{array}{c} \text{alfated} \\ \text{angstate} \\ \text{S/110 °C/8h} \end{array} \begin{array}{c} \text{S} \\ \text{R}_1 \\ \text{R}_2 \\ \text{R}_3 \\ \text{R}_3 \end{array} \right) $			
Entry	R ₁	R ₂	R ₃	Product	Yield
1	C ₆ H ₅	Н	Н	NH ₂	76 ^b
2	4-MeOC ₆ H ₄	н	н	H ₃ CO NH ₂	60 ^b
3	4-CIC ₆ H ₄	н	Н	CI NH2	63 ^b
4	$3-O_2NC_6H_4$	Н	Н	NH ₂ NO ₂	66 ⁵
5	$4-O_2NC_6H_4$	Н	Н	O ₂ N NH ₂	56 ^b
6	C ₆ H ₅	C ₆ H ₅	Н	S N	90
7	C ₆ H ₅	4-MeC ₆ H ₄	Н	S N CH3	90
8	C ₆ H ₅	4-MeOC ₆ H ₄	Н	S N CCH3	90
9	C ₆ H ₅	4-ClC ₆ H ₄	Н	S N CI	81
10	C ₆ H ₅	2-CIC ₆ H ₄	Н	S N CI	70
11	C ₆ H ₅	C ₆ H ₅ CH ₂	Н	S H H	91
12	C ₆ H ₅	$C_6H_5CH_2CH_2$	Н	N C	84
13	C ₆ H ₅	c-Hex	Н	S N	90

Table 5 (Continued)

Entry	R ₁	R ₂	R ₃	Product	Yield
14	4-HOC ₆ H ₄	C ₆ H ₅	Н	HO	85
15	4-MeOC ₆ H ₄	C ₆ H ₅	Н	H ₃ CO	88
16	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	Н	H ₃ CO	89
17	C ₆ H ₅	2-pyridyl	Н	S N N	82
18	C ₆ H ₅	3-pyridyl	н	S NH	84
19	2-furyl	c-Hex	Н	S NH	90
20	2-thiophenyl	C ₆ H ₅	Н	S NH	89
21	2-methylpropyl	c-Hex	Н	S H H	90
22	C ₆ H ₅	-(CH ₂) ₅ -		S N	91
23	C ₆ H ₅	-(CH ₂) ₂ -0-(CH ₂) ₂ -		S N O	89

^a Conditions: benzaldehyde (1.0 equiv), aniline (1.25 equiv), sulfur (1.25 equiv) and catalyst (10 wt%) at 110 °C in DMF.

^b Ammonia as ammonium acetate.

3. Result and discussion

Initial investigations were carried out on thioamidation reaction using benzaldehyde and aniline as building blocks (Scheme 1).

Reactions were carried out at different temperatures in DMF and the best results were obtained at $110 \,^{\circ}$ C where as, yields were lower at 60 $\,^{\circ}$ C and 90 $\,^{\circ}$ C and reaction did not proceed at room temperature (Table 1, entries 6–8). Investigations were also carried out to establish the catalytic role and optimize quantity of sulfated tungstate. A reaction was carried out in the absence of sulfated tungstate and it was found that, the reaction was very slow and gave just 15% yield, in 24 h (Table 1, entry 1). Whereas the same reaction in presence of 10 wt% of sulfated tungstate, got accelerated, to give a yield of 90% in 8 h thus establishing catalytic role of sulfated tungstate (Table 1, entry 4). To optimize catalyst amount, a set of reactions were carried out with increasing amounts of catalyst in the range of 1–20 wt%. From the results (Table 1, entries 2–5), it was concluded that an amount of 10 wt% is optimum giving maximum yield and further increase in quantity did not show any benefits. Reaction under study did not show encouraging results under solvent-free condition either in absence or presence of the catalyst even at $110 \,^{\circ}$ C (Table 1, entries 9 and 10). The reaction was investigated using other polar solvents such as DMSO, NMP respectively, however in both cases, reaction was comparatively slow and gave lower yields even after 12 h (Table 1, entries 11 and 12). Other solvents like toluene, acetonitrile and water were also investigated but in all cases practically there was no reaction.

To optimize mole ratio of substrates, experiments were performed with 10 wt% of catalyst and varying ratios of substrates and results are given in Table 2. The reaction with equimolar quantities of benzaldehyde, aniline and sulfur shows 76% yield of *N*-phenylbenzothioamide (Table 2, entry 1). With further investigations optimum mol ratio was arrived at 1:1.25:1.25 of aldehyde:aniline:sulfur respectively giving 90% yield (Table 2, entry 3) and was chosen for further studies. Increasing mole ratio of aniline and sulfur to 1.5 and 2 equiv respectively did not show significant improvement in yields (Table 2, entries 4 and 5). When aldehyde was in excess over the aniline, yields were only 74% (Table 2, entries 6).

To assess the standing of the catalyst, amongst other acid catalysts, a comparative study was performed and results are given in Table 3. The yield obtained using sulfated tungstate was very high and even with lesser amount as compared to other acid catalysts thus indicating its superiority.

Reusability study was performed, and results presented in Table 4, indicate that the catalyst was stable and reusable four times without any loss of activity. It is noteworthy that the catalyst was recovered simply by filtration without any acidic or basic workup even after its fourth use.

In order to prove that the reaction is heterogeneous, a standard leaching experiment was conducted. Two sets of experiments were conducted and both reactions were proceeded for 1 h. One experiment was worked up, while from the other, the catalyst was filtered off and the reaction was continued at the same reaction temperature of 110 °C for 12 h and worked up. The yields obtained in both cases 8% and 11% respectively, were practically same, indicating that no homogeneous catalyst was involved.

To explore generality and scope of the method, variety of substrates was used to synthesize primary, secondary and tertiary thioamides and results are shown in Table 5. The method was found to be suitable, but with low yields, for preparation of primary thioamides with benzaldehydes, containing electron donating as well as electron withdrawing groups and ammonia as ammonium acetate (Table 5, entries 1–5). This is noteworthy feature because, there are only few reports concerning the synthesis of primary thioamide by Kindler reaction [39–41]. To investigate substituent effect, benzaldehydes and anilines, both variously substituted, were reacted. In all cases, irrespective of substituent being electron withdrawing or electron donating, reactions were smooth and gave excellent yields (Table 5, entries 7–8 and 11–13).

In case of halogenated benzaldehdyes, halogen remained intact and no side products were observed arising from reactions with amines and sulfur (Table 5, entries 3, 9 and 10). Slightly lower yields were observed with, sterically hindered, 2-chloroaniline (Table 5, entry 10). Under similar set of conditions, interestingly, aliphatic amines and aldehydes gave excellent yields of the respective thioamides (Table 5, entries 11-13, 19 and 21). The catalyst, sulfated tungstate, was also effective for the reaction of benzaldehyde and heteroaromatic amines (Table 5, entries 17 and 18). Substrates containing methoxy and phenolic groups were compatible under the reaction conditions (Table 5, entries 2, 8, 14-16). Even the furan ring, which is prone to polymerization under acidic condition, was stable and furfural reacted smoothly gave excellent yield (Table 5, entry 19). Reaction with thiophene aldehyde was also equally facile (Table 5, entry 20). As expected, cyclic secondary amines viz. piperidine, morpholine reacted equally well and gave high yields (Table 5, entries 22 and 23). Thus the protocol developed represents an efficient, improved and cost effective methodology for Kindler reaction.

4. Conclusion

Sulfated tungstate was found to be suitable as catalyst for Kindler reaction for synthesis of primary, secondary and tertiary thioamides in high yields. The remarkable catalytic activity exhibited by sulfated tungstate is superior to other reported methods with respect to operational simplicity, cleaner reaction profile. The catalyst is, green, easy to recover and reusable and holds potential for large scale applications.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.apcata.2012.03.012.

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