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## Graphical Abstract

**Sulfated Tungstate Catalyzed Activation of Nitriles: Addition of Amines to Nitriles for Synthesis of Amidines**

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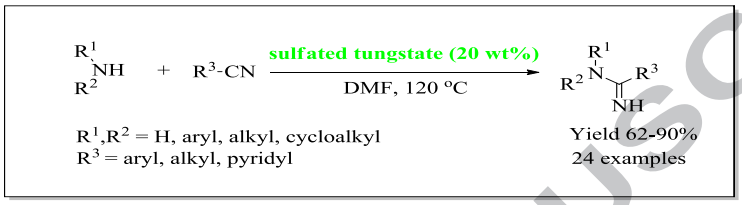

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# Sulfated tungstate catalyzed activation of nitriles: addition of amines to nitriles for synthesis of amidines

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ABSTRACT

An efficient and mild method for synthesis of amidines by direct nucleophilic addition of amines to nitriles using sulfated tungstate as heterogeneous catalyst is described. High light of the method is its applicability for synthesis of amidines using wide variety of amines including ammonia as ammonium acetate and nitriles. Catalyst is mildly acidic, stable, easy to prepared and separate from reaction mass.



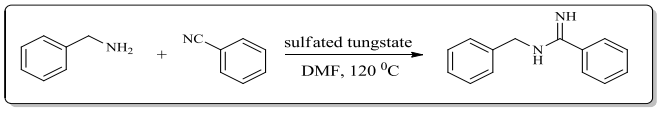
## Introduction

Amidines are of immense value in organic synthesis[1-2]. For medicinal chemists amidine is a potent pharmacophore unit for drug design, and also amidines are intermediates for construction of heterocyclic moieties and active pharmaceutical ingredients such as pentamidine and furamidine[3]. Amidines are widely used as building blocks in synthesis of heterocycles[4] such as 1,2,4-thiadiazoles[4a], imidazoles[4b], aminophenanthridines[4c], pyrimidinones[4d], pyridines[4e], purines[4f], pyrimidines[4g], triazaphenalenes[4h], triazines[4i], tetrazoles[4i], thiadiazines[4j], oxazolotriazoles[4k], and diazirines[4l], which have applications in many fields[5-6]. There are different strategies for synthesis of amidines including reductive deprotection of *O*-benzylamidoximes[7], catalytical addition of terminal alkynes to carbodiimides[8], and nucleophilic addition of amines to nitriles[9]. Ready availability of variety of amines and nitriles makes nucleophilic addition of amines to nitriles as useful strategy for synthesis amidines. Moreover, it is one of the simplest methods and has 100% atom economy. Direct addition to amines to nitriles has always been a challenge, especially, if nitriles are not activated. The additions are made possible when nitriles are activated either by electron withdrawing groups[10] or by employing forcing conditions in the presence of Lewis acids[11] such as $AlCl_3$[11a], $ZnCl_2$[11a], aluminium amide[11b], $CaCl_2$[11c], $SmI_2$[11d] and Ytterbium amide[11e]. Alternatively, amidines are made available from corresponding nitriles via imidate formation as in Pinner synthesis[12]. This clearly indicates that there is scope for development of heterogeneous solid acid catalyst for synthesis of amidines.

Our group has successfully developed sulfated tungstate, a mildl acidic, non corrosive, stable, reusable, heterogeneous, green catalyst for many organic transformations like amidation and formylation[13]. Sulfated tungstate is an amorophus powder with surface area of 1.9 $m^2$ $g^{-1}$, particle size 1.49 µm, thermally stable up to 200 °C, acidity is 373 mV which is greater than that of silicagel and tungstic acid with elemental distribution mapping by EDAX showing tungsten: oxygen: sulfur signal ratio of 69.13: 30.55: 0.31 wt%. Many of these reactions use amines as one of the reactants as in amidation by direct reaction between carboxylic acids and amines[13a], Willgerodt-Kindler reaction for synthesis of thiomorpholides[13b], Strecker synthesis[13c], Kindler reaction[13d], *N*-formylation[13e], transamidation[13f] and *N*-monoalkylation of primary amines[13g]. In all these reactions it has been observed that nucleophilicity of amines was not compromised and reactions were facile giving high yields, clearly indicating activation of electrophilic counter part by the catalyst. In the present work this feature of the catalyst is exploited to activate nitriles by sulfated tungstate without compromising on nucleophilicity of amines, leading to facile addition of amine to form amidines with added advantage is heterogeneous nature of the catalytic reaction and easy work up procedure.

## Results and Discussion

Preliminary investigations were conducted using 1:1 mole ratio of benzylamine and benzonitrile as building blocks and DMF as solvent (Scheme 1).




**Scheme1.** Synthesis of *N*-benzylbenzimidamide from benzylamine and benzonitrile

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Reactions were carried out using 20 wt% of sulfated tungstate at different temperatures of rt, 50 °C, 80 °C, 100 °C and 120 °C. Amidine formation was observed at 80 °C but at very slow rate and gave 18% yield in 24 h (Table 1, entry 3), whereas at 120 °C the reaction was faster and gave 90% yield of *N*-benzylbenzamidine in 12 h (Table 1, entry 5). Therefore further studies were conducted at 120 °C.

To identify the influence of sulfated tungstate on the reaction and how much amount is optimum, a set of reactions were carried out with subsequently increasing amounts in the range of 0-30 wt%. From the results, it was concluded that sulfated tungstate is required for the reaction, because in the absence of it the reaction did not occur (Table 1, entry 6). A 20 wt% was found optimum amount because further increase in quantities did not show any advantage (Table 1, entry 12).

**Table 1.** Optimization of reaction conditions[a]

| Entry | Sulfated tungstate (wt%) | Temperature [°C] | Time [h] | Yield[b] |
|---|---|---|---|---|
| 1 | 20 | rt | 24 | NR[c] |
| 2 | 20 | 50 | 24 | NR[c] |
| 3 | 20 | 80 | 24 | 18 |
| 4 | 20 | 100 | 24 | 58 |
| 5 | 20 | 120 | 12 | 90 |
| 6 | - | 120 | 12 | NR[c] |
| 7 | 5 | 120 | 12 | 38 |
| 8 | 10 | 120 | 12 | 56 |
| 9 | 15 | 120 | 12 | 78 |
| 10 | 20 | 120 | 12 | 90 |
| 11 | 25 | 120 | 12 | 91 |
| 12 | 30 | 120 | 12 | 90 |

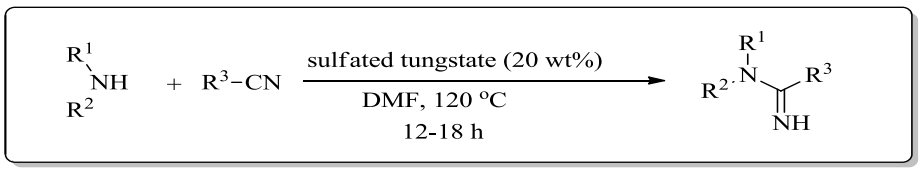
[a]Reaction condition: benzylamine (1 g, 9.34mmol) and benzonitrile (0.96 g, 9.34 mmol) in DMF as a solvent. [b]Isolated yield, [c]NR= No reaction.

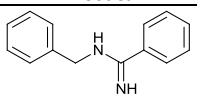
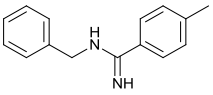
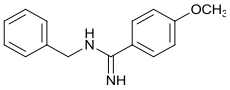
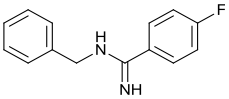
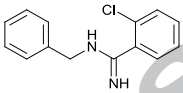
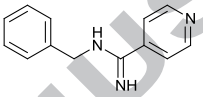
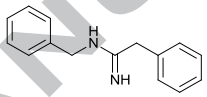
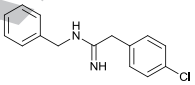
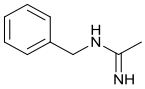
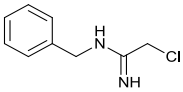
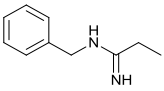
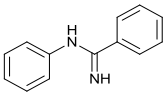
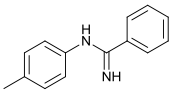
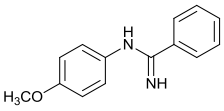
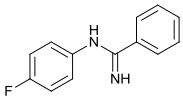
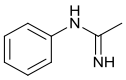
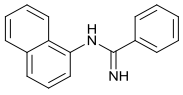
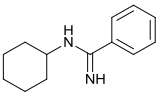
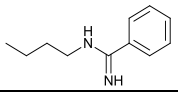
To explore the generality and scope of the method, reactions were examined with structurally diverse aromatic and aliphatic, amines and nitriles, as shown in Table 2.

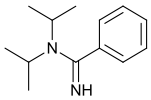
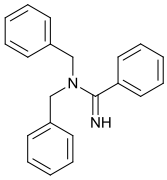
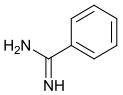
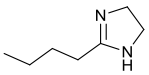
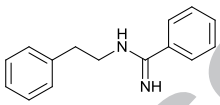
Considering amines as counterpart reactions of benzylamines with variety of nitriles, both aliphatic, aromatic and heteroaromatic, were smooth and gave corresponding amidines in high yields (Table 2, entries 1-11). Reactions between aromatic amines, including anilines and 1-naphthylamine and benzonitrile were viable but reactions were very slow giving comparatively lower yields in 18h (Table 2, entries 12-17). Many aliphatic amines including primary *n*-butylamine and phenylethylamine, sterically hindered secondary diisopropylamine, and dibenzylamine, cyclohexylamine reacted well with benzonitrile giving corresponding amidines in comparable yields (Table 2, entries 18-21 and 24). It is note worthy that ethylene diamine on reaction with veleronitrile gave expected imidazoline in high yield of 80% (Table 2, entry 23) by first forming amidines followed by cyclisation to form five membered ring. Imidazoline moiety is found in many drugs including losartan, eprosartan and etomidate[14]. Therefore this method could be very valuable for their synthesis. Significant result is the formation of benzamidine by reaction between ammonium acetate and benzonitrile (Table 2, entry 22) indicating that method could be useful for synthesis of even unsubstituted amidines. All these results clearly establish the suitability of the method for wide variety of amines including ammonia as ammonium acetate. As far as nitriles counterpart is concerned, reactions were possible with both aromatic and aliphatic nitriles. Aromatic nitriles (Table 2, entries 1-5, 7-8, 12-15, 17-22, 24) including heteroaromatic nitrile (Table 2, entry 6), reacted smoothly. In all cases yields were better with unsubstituted benzonitrile giving highest yield of 90% with benzylamine (Table 2, entry 1). Steric effect, typical of ortho substituents as in case of *o*-chlorobenzonitrile, was not observed and the reaction between benzylamine and *o*-chlorobenzonitrile was equally facile giving 85% yield in the same reaction time of 12 h (Table 2, entry 5). Reactions of acetonitrile with benzylamine and aniline were also possible however yield was slightly lower in case of reaction between acetonitrile and aniline giving 65% (Table 2, entries 9 and 16). Reaction between chloroacetonitrile and benzylamine gave chloroacetamidine (Table 2, entry 10). This result is significant because, the method shows chemoselectvity with chlorine not getting displaced and α-chloroamidines are useful synthons for construction of heterocycles[15].

In conclusion, it can be said that a one-step protocol for synthesis of amidines by nucleophilic addition of amines to nitriles in presence of sulfated tungstate as mild, chemoselective, stable, heterogeneous catalyst has been developed. High light of the method is its applicability for synthesis of amidines using wide variety of amines including ammonia as ammonium acetate and nitriles.

**Table 2.** Synthesis of amidines of different classes of amines and nitriles using sulfated tungstate as catalyst



| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Time (h) | Yield[b] |
|---|---|---|---|---|---|---|
| 1 | $PhCH_2$ | H | Ph |  | 12 | 90 |
| 2 | $PhCH_2$ | H | *p*-$CH_3$-Ph |  | 12 | 82 |
| 3 | $PhCH_2$ | H | *p*- $H_3CO$ -Ph |  | 12 | 80 |
| 4 | $PhCH_2$ | H | *p*-F-Ph |  | 12 | 88 |
| 5 | $PhCH_2$ | H | *o*-Cl-Ph |  | 12 | 85 |
| 6 | $PhCH_2$ | H | 4-pyridinyl |  | 12 | 82 |
| 7 | $PhCH_2$ | H | $PhCH_2$ |  | 16 | 80 |
| 8 | $PhCH_2$ | H | *p*-Cl-$PhCH_2$ |  | 16 | 82 |
| 9 | $PhCH_2$ | H | $CH_3$ |  | 12 | 78 |
| 10 | $PhCH_2$ | H | Cl-$CH_2$ |  | 12 | 82 |
| 11 | $PhCH_2$ | H | $CH_3CH_2$ |  | 12 | 75 |
| 12 | Ph | H | Ph |  | 18 | 70 |
| 13 | *p*-$CH_3$-Ph | H | Ph |  | 18 | 62 |
| 14 | *p*-$H_3CO$-Ph | H | Ph |  | 18 | 68 |
| 15 | *p*-F-Ph | H | Ph |  | 18 | 72 |
| 16 | Ph | H | $CH_3$ |  | 18 | 65 |
| 17 | 1-naphthyl | H | Ph |  | 18 | 68 |
| 18 | *cyclo*-$C_6H_{11}$ | H | Ph |  | 18 | 72 |
| 19 | $CH_3(CH_2)_3$ | H | Ph |  | 18 | 75 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 20 | $(CH_3)_2CH$ | $(CH_3)_2CH$ | Ph |  | 18 | 63 |
| 21 | $PhCH_2$ | $PhCH_2$ | Ph |  | 12 | 76 |
| 22[d] | H | H | Ph |  | 18 | 68 |
| 23 | $H_2N(CH_2)_2$ | H | $CH_3(CH_2)_3$ |  | 16 | 80 |
| 24 | $Ph(CH_2)_2$ | H | Ph |  | 12 | 72 |

[a]Reaction conditions: amine (1.0 equiv), nitrile (1.0 equiv) and sulfated tungstate (20 wt% ) at 120 °C,in DMF as solvent. [b]Isolated yield. [d]Ammonia is used as ammonium acetate. [c]All products are known and were identified by their melting point, IR and $^1$HNMR spectra, according to the literature.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16. Sulfated tugstate was prepared as per the reported procedure.[13a]
General:$^1$H NMR (300 MHz)of all the products were recorded at 300MHz in $CDCl_3$ as solvent and chemical shift values are expressed in δ units relative to tetramethylsilane ($Me_4Si$) signal as internal reference in $CDCl_3$. IR spectra were recorded as KBr pellet. Purity of all compounds was established using the common HPLC conditions: isocratic elution: (0.05% $CF_3COOH$, Water/$CH_3CN$ 50:50), flow rate = 1.0 mL/min, T = 25 °C, UV detection at 254 nm with column Purosphere, RP-18e (5μm).
All the solvents were purchased from commercial sources and were used without further purification.
**Procedure for sulfated tungstate mediated synthesis of *N*-benzylbenzamidine (Table 2 entry 1)**
Sulfated tungstate (0.2 g, 20 wt%) was added to a mixture of benzylamine (1 g, 9.34 mmol) and benzonitrile (0.96 g, 9.34 mmol) in DMF(10 ml) and stirred at 120 °C for 12 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to rt and filtered, washed with ethyl acetate to recover the catalyst. Combined filtrate and washings were concentrated under reduced pressure and the residue obtained was chromatographed (silica gel #60-120; eluent: hexane-ethyl acetate = 40 : 60) to get pure *N*-benzylbenzamidine as white solid.;Yield:1.77 g 90%, white solid, mp 75-77 °C (lit[17] 77-78 °C). IR (KBr) 3287, 3035, 2868, 1662, 1534, 1385, 1241, 725, 699 cm$^{-1}$. $^1$H NMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 7.31-7.22 (m, 10 H), 5.89 (s, 1 H), 4.50 (d, J=8.4Hz, 2H), 1.80 (s, 1 H). HPLC retention time: 2.33 min.
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**Supplementary Material**

Supplementary data (experimental procedures, characterization data and copies of IR and $^{1}H$ NMR spectra of ethers) associated with this article can be found, in the online version, athttp://dx.doi.org/10.1016/j.tetlet.XXXX

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Highlights

- The catalyst is well characterized, reusable, stable, easy to prepare, mildly acidic and non corrosive solid.
- Mild reaction conditions and easy work up procedure.
- The catalyst activates nitriles without compromising nucleophilicity of amines.
- The method is applicable for synthesis of amidines using wide variety of amines and nitriles.
- Amidines are very useful substrates in organic synthesis and medicinal chemistry.