One-pot three-component synthesis of a-amino nitriles catalyzed by Molybdate Sulfuric Acid (MSA)

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ABSTRACT

The molybdate sulfuric acid (MSA) was found to efficiently catalyze for the synthesis of α-amino nitriles from aldehydes, amines and trimethylsilyl cyanide under a solvent-free condition in high yield with short reaction times.   © 2015 Trade Science Inc. - INDIA
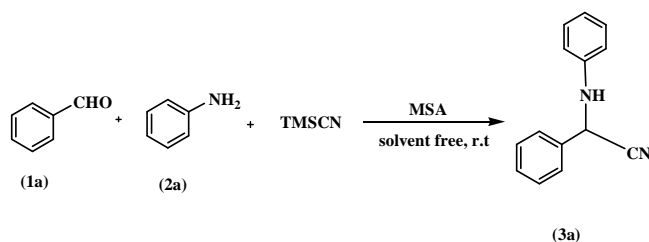
INTRODUCTION

Three-component Strecker-type reaction from carbonyl compounds, amines, and trimethylsilyl cyanide (TMSCN) is an important reaction in organic synthesis because the products, α-aminonitrile derivatives, are versatile intermediates, which can be transformed into various building blocks, including a-amino acids, 1,2-diamines, and nitrogen-containing heterocycles[1]. Various Lewis acids such as $Yb(OTf)_3$,[2] $Pr(OTf)_3$,[3] $Cu(OTf)_2$,[4] $LiClO_4$,[5] $BiCl_3$,[6] $NiCl_2$,[7] $RuCl_3$,[8] $CeCl_3$,[9] InI_3,[10] RhI_3,[11] $La(NO_3)_3.6H_2O$ or $GdCl_3.6H_2O$,[12] iodine,[13] and (bromodimethyl) sulfonium bromide,[14] homogeneously catalyze the Strecker-type reaction. However, the reaction usually demands high catalyst loadings (>10 mol%), long reaction times ranging from several hours to several days in some cases, strong acidic conditions, expensive and hazardous reagents.

RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents[15-21], we wish, herein, to report on the use of MSA as a more robust and efficient catalyst for the synthesis of α-amino nitriles **(3a-j)** from aldehydes, amines and trimethylsilyl cyanide under a solvent-free condition.

At first, we studied the reaction of benzaldehyde **(1)** with aniline **(2)** and trimethylsilyl cyanide in order to optimize the reaction conditions with respect to temperature and molar ratio of MSA to the substrate. We found that 5 mol % of MSA was sufficient to produce the desired 2-(*N*-anilino)-2-phenylacetonitrile **(3a)** in
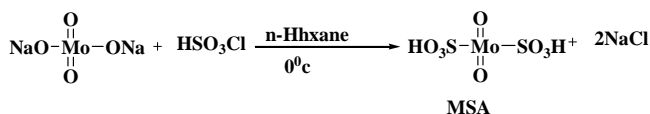

Scheme 1 : Synthesis of α-amino nitriles using MSA

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95% yield within 5 min in solvent free at room temperature (Scheme 1).

Molybdate sulfuric acid is an easily prepared and moisture tolerant solid acid which has been used as catalyst in the oxidation of thiols and nitrosation of amines[22,23]. The reusability of catalyst is an important factor for commercial uses. Therefore, the recovery and reusability of MSA was investigated. Hence, MSA was successfully regenerated from the model reaction by washing with EtOAc and drying at 120 °C. Attempts to the reusability of MSA showed that reactivity of the recovered catalyst was efficiently depending on the solvent applied for regeneration of catalyst. However, washing the filtered catalyst from the first run by warm protic solvents such as water and alcohols resulted in the obvious decreasing of reaction yield. In the contrast, the recycled catalyst by EtOAc was reused three times with gradual loss of activity in the model reaction. (Scheme 2)

$$NaO-\overset{O}{\underset{O}{\overset{\|}{Mo}}}-ONa + HSO_3Cl \xrightarrow[0^0c]{n-Hhxane} HO_3S-\overset{O}{\underset{O}{\overset{\|}{Mo}}}-SO_3H + 2NaCl$$

MSA

Scheme 2 : Preparation of MSA Catalyst

After optimizing these conditions using benzaldehyde as a model aldehyde, the reactions were performed with various other aryl aldehydes, and it was noticed that the reaction proceeds well with all types of aryl aldehydes and the results of this study are presented in TABLE 1.

EXPERIMENTAL

Chemicals were obtained from Merck and Fluka chemical companies. The IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained in CDCl$_3$ using a 400 MHz JEOL FT NMR spectrometer. All melting points were determined on an Electro Thermal 9100 melting point apparatus.
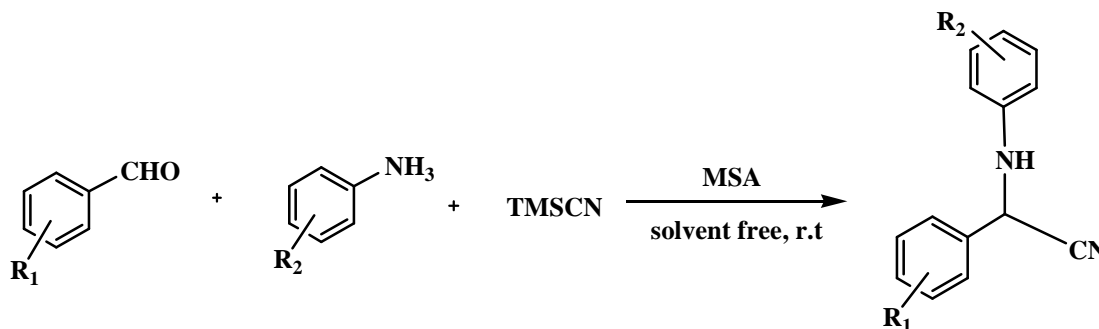
Preparation of catalyst

MSA was prepared via a modified version of the previously reported procedures (Scheme 2). Thus, anhydrous sodium molybdate (20 mmol, 4.118 g) was added to dry n-hexane (25 mL) in a 100 mL round

bottom flask equipped with ice bath and overhead stirrer. Chlorosulfonic acid (0.266 mL, 40 mmol) was then added dropwise to the flask during 30 min and stirred for 1.5 h. The reaction mixture was gradually poured into 25 mL of chilled distilled water with agitation. The molybdate sulfuric acid was separated as a bluish solid by filtra-tion, washed with cold distilled water five times until the negative test for chloride ion for filtrate, and dried at 120 °C for 5 h. The yield of the obtained bluish acid catalyst was 90%.

Characterization of catalyst

The prepared catalyst was characterized by determination of decomposition point, FT-IR spectrum, and neutralization titration with standard solution of NaOH. As a result, the prepared molybdate sulfuric acid which showed good thermal stability decomposed at 354 °C. The overlaid FT-IR spectra of sodium molybdate and molybdate sulfuric acid (MSA) are shown in Figure 1. As the spectrum of MSA demonstrates, the characteristic bands of both anhydrous sodium molybdate and -OSO$_3$ group are shifted evidently to the higher wave numbers. The well defined bands at 3600–3000 is related to OH stretching, the band at 1635 cm^{-1} is the H-O-H bending mode of the lattice water, and the bands at 1300–1100 cm^{-1} might be the asymmetric and sym-metric stretching modes of S=O. A strong band at 827 cm^{-1} in the FT-IR spectrum of sodium molybdate is assigned to the stretching mode of Mo-O. This band is shifted to ~1100 cm^{-1} and appeared as an overlapped band with S=O stretching bands in spectrum of MSA. Broadening of the absorbance band positioned at 3600–3000 cm^{-1} is due to the rapid exchanges of acidic hydrogens via H-bonding and reveals the formation of MSA. In order to investigate the acid capacity of MSA, a solution of it (0.0805 g) in distilled water (100 mL) was titrated with standard solution of NaOH (0.1 N) in the presence of phenolphthalein as indicator. At the endpoint of titration 5 mL of titrant was consumed. The capacity of MSA was determined according the following equation as 2. $(m/MW) \times n = N_2V_2$, $(0.0805/322) \times n = 0.1 \times 0.005$, thus n = 2. Therefore, MSA can be considered as a solid heterogeneous alternative to sulfuric acid.

General procedure for the synthesis of α-amino

TABLE 1 : Synthesis of α-amino nitriles using MSA under solvent free conditions

$$\text{R}_1\text{-C}_6\text{H}_4\text{-CHO} + \text{R}_2\text{-C}_6\text{H}_4\text{-NH}_3 + \text{TMSCN} \xrightarrow[\text{solvent free, r.t}]{\text{MSA}} \text{product}$$

Entry	Product	R$_1$	R$_2$	Time (min)	Yelde (%)	M.P (°c)
1	3a	C$_6$H$_5$	aniline	7	95	83-84
2	3b	4-ClC$_6$H$_4$	aniline	5	90	105-107
3	3c	4-BrC$_6$H$_4$	aniline	6	96	99-101
4	3d	4-MeC$_6$H$_4$	aniline	9	90	90-92
5	3e	4-OMeC$_6$H$_5$	aniline	11	96	95-97
6	3f	C$_6$H$_5$	4-methylaniline	15	94	88-90
7	3g	4-ClC$_6$H$_4$	4-methylaniline	12	92	100-102
8	3h	4-BrC$_6$H$_4$	4-methylaniline	12	94	97-99
9	3i	C$_6$H$_5$	4-methoxyaniline	14	97	81-83
10	3j	4-BrC$_6$H$_4$	4-methoxyaniline	11	91	89-91

a) All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples b) Isolated yields. c) Melting points of compounds are consistent with reported values[24,25].
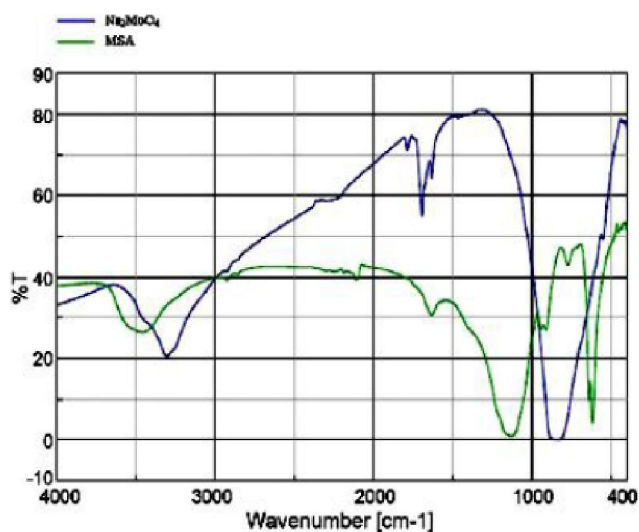

Figure 1 : Overlaid FT-IR spectra of Na$_2$MoO$_4$ and H$_3$OSO(MoO$_2$)OSO$_3$H (MSA)

nitriles in solid-state catalyzed by MSA

A mixture of aldehydes (1.0 mmol), amines (1.0 mmol) and MSA (5 mol %) were added to a mortar and the mixture was pulverized with a pestle. A spontaneous reaction took place [7-15 min, TABLE 1, monitored by TLC (4:1, hexane/ acetone)]. After completion of the reaction, CH$_2$Cl$_2$ (10 mL) was added, and insoluble reagents were removed by filtration. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by recrystallization from ethanol to afford pure products.

CONCLUSION

In conclusion, a new strategy has been developed

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for the synthesis of α-amino nitriles from aldehydes, amines and trimethylsilyl cyanide using MSA as a highly efficient catalyst. The notable advantages of this methodology are mild conditions, short reaction times, high yields, and the absence of side products. This method offers one of the important motifs for synthesis of α-amino nitriles, as natural products, biologically active compounds, and pharmaceutical agents.

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