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Sulfamic acid: an efficient, cost-effective and recyclable solid acid catalyst for the three-component synthesis of α-amino nitriles

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Abstract—α-Amino nitriles are synthesized by the three-component coupling reaction of aldehydes, amines and trimethylsilyl cyanide using sulfamic acid as a heterogeneous solid acid catalyst, under solvent-free conditions in excellent yields. The catalyst was recovered by simple filtration and was recycled in subsequent reactions.

α-Amino nitriles, are important precursors in the synthesis of natural and unnatural α-amino acids, various nitrogen-containing heterocycles[1] and other biologically useful molecules such as saframycin A.[2] The Strecker reaction is well known, yet its course depends on the catalyst used. Many catalysts have been used to promote the Strecker reaction including: lithium perchlorate,[3] scandium triflamide,[4] vanadyl triflate,[5] nickel(II) chloride,[6] zinc halides,[7] ruthenium(III) chloride,[8] ytterbium triflate,[9] bismuth(III) chloride,[10] $H_{14}[NaP_5W_{30}O_{110}]$,[11] Montmorillonite KSF,[12] $Cu(OTf)_2$[13] and indium trichloride.[14] No reaction was observed in the absence of catalyst. In some cases, the protocols involve the use of strong and expensive Lewis acids, harsh conditions and tedious aqueous work-up leading to the generation of large amounts of toxic metal-containing waste. Moreover, some of the Lewis acids used are, like their hydrolysis products, toxic. Hence, there is further scope to explore milder, safer and more efficient protocols for this reaction. In recent years, the use of solid acids as heterogeneous catalysts has received significant interest in different areas of organic synthesis.[15] Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby making the process economically more viable. We herein report a recyclable, easily separable and highly effective catalytic system (sulfamic acid (SA)/solvent-free or SA/MeOH) for the synthesis of α-amino nitriles under mild reaction conditions. Sulfamic acid (H_2NSO_3H) is an amino acid-containing sulfur element with mild acidity, involatility and is non-corrosive and is utilized as a stable, low-cost, highly efficient green catalyst in organic synthesis.[16]

The catalytic features and intrinsic zwitterionic property of SA is very different from conventional acidic catalysts, which encouraged us to investigate further applications of SA as an acidic catalyst in other carbon–carbon and carbon–heteroatom bond forming reactions. Herein, we describe a mild and efficient protocol for the synthesis of α-amino nitriles using a catalytic amount of sulfamic acid under solvent-free conditions at ambient temperature.

In the presence of 5 mol % sulfamic acid, the three-component coupling reaction involving benzaldehyde, aniline and trimethylsilyl cyanide afforded the corresponding α-amino nitrile (**4a**) in 98% yield (Scheme 1). Several α-amino nitriles were prepared using this methodology as shown in Scheme 1. This one-pot process can be defined as a Strecker reaction between imines or iminium ions and TMSCN. Aliphatic, aromatic, heterocyclic and conjugated aldehydes[15] afforded the desired products in high yields. The method worked very well for acid sensitive aldehydes such as furfural and also for enolizable aldehydes (entry f). The best results were obtained using both primary and secondary amines. In all cases, no undesired side products such as cyanohydrins

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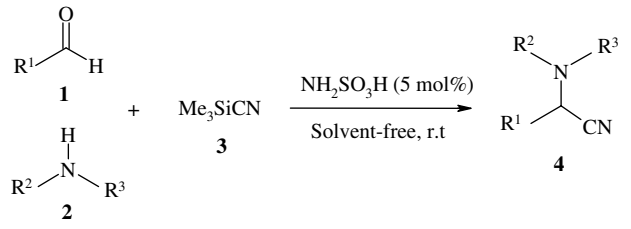

entry	R^1	R^2	R^3	yield (%) of **4**
a	Phenyl	H	Phenyl	98
b	*n*-butyl	H	Phenyl	90
c	4-Me-Phenyl	H	Phenyl	97
d	2-Furyl	H	Phenyl	95
e	Cinnamyl	H	Phenyl	98
f	*n*-butyl	Ethyl	Ethyl	82
g	Phenyl	Ethyl	Ethyl	90
h	4-Me-Phenyl	Ethyl	Ethyl	85
i	2-Furyl	Ethyl	Ethyl	80
j	Cinnamyl	Ethyl	Ethyl	88
k	4-MeO-Phenyl	Ethyl	Ethyl	91
l	Phenyl	Benzyl	Benzyl	94
m	*i*-Propyl	Benzyl	Benzyl	94
n	4-Me-Phenyl	*tert*-butyl	H	84
o	Cinnamyl	*tert*-butyl	H	88

Scheme 1.

were obtained under these conditions. We believe that this is mainly due to the rapid formation and activation of the imine intermediates catalyzed by sulfamic acid. Higher amounts of catalyst did not improve the yields. The insolubility of the SA catalyst in different organic solvents provides an easy method for separation of the catalyst and the product. The catalyst was separated by filtration and reused after activation with only a gradual decrease in activity observed. For example, the reaction of benzaldehyde (**1a**), aniline (**2a**) and trimethylsilyl cyanide (**3**) gave the corresponding α-amino nitrile (**4a**) in 98%, 96% and 92% yields over three cycles.

In conclusion, this method provides an easy access to α-amino nitriles with a wide range of substitution patterns and offers several advantages, such as higher yields, shorter reaction times, cleaner reaction profiles and simple experimental and work-up procedures. All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy. Although the amount of catalyst has been optimized to 5 mol %, a smaller amount (3 mol %) also worked but required a longer reaction time.

General procedure: Solvent-free: a mixture of aldehyde (3 mmol), amine (3.2 mmol), trimethylsilyl cyanide (3 mmol) and sulfamic acid (5 mol %) was stirred vigorously at room temperature for an appropriate amount of time (5–30 min). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloromethane (3×10 mL). The combined organic layers were concentrated under vacuum and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane) to afford pure α-amino nitriles. The recovered catalyst was washed with diethyl ether, dried and reused for subsequent runs.

^{1}H NMR, ^{13}C NMR and IR were consistent with the assigned structures and were compared with those reported in the literature. Spectral data for selected products: Compound **4a**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.1$ (br s, 1H, NH), 5.4 (s, 1H), 6.5–6.8 (m, 5H), 7.1–7.8 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 48.2$, 114.3, 117.8, 128.2, 128.3, 129.2, 131.4, 145.5. Compound **4d**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 4.1$ (br s, 1H, NH), 5.4 (s, 1H), 6.3–6.5 (m, 3H), 7.1–7.8 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 47.3$, 102.3, 113.8, 114.6, 116.1, 118.0, 130.0, 133.4, 139.0, 147.8. Compound **4e**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.9$ (br s, 1H, NH), 5.0 (d, $J = 4.5$ Hz, 2H), 6.3 (dd, $J = 7.8$ Hz, 4.5 Hz, 1H), 6.9 (d, $J = 7.8$ Hz, 2H), 6.1–6.8 (m, 5H), 7.1–7.8 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 46.4$, 114.3, 117.0, 118.6, 119.9, 126.0, 127.1, 129.3, 131.1, 132.0, 135.2, 146.2. Compound **4i**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.1$ (t, $J = 8.7$ Hz, 6H), 2.5 (*q*, $J = 8.7$ Hz, 4H), 5.0 (s, 1H), 6.2–6.4 (m, 2H), 7.5 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.2$, 48.2, 52.0, 96.3, 106.3, 145.0, 153.4. Compound **4l**: ^{1}H NMR (500 MHz, $CDCl_3$): 3.44 (d, $J = 13.4$ Hz, 2H), 3.8 (d, $J = 13.4$ Hz, 2H), 4.9 (s, 1H), 7.0–7.2 (m, 4H), 7.35–7.4 (m, 9H), 7.53–7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.4$, 54.0, 55.6, 116.0, 126.0, 127.8, 128.3, 129.0, 130.5, 131.3, 133.9, 145.7.

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