



# Highly efficient and convenient Strecker reaction of carbonyl compounds and amines with TMSCN catalyzed by MCM-41 anchored sulfonic acid as a recoverable catalyst

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## ABSTRACT

MCM-41 anchored sulfonic acid (MCM-41–SO<sub>3</sub>H) was found to be a highly efficient and recoverable heterogeneous catalyst for the three-component Strecker reaction of aldehydes or ketones and diverse amines using trimethylsilyl cyanide (TMSCN) to afford the corresponding  $\alpha$ -amino nitriles under mild conditions in high to quantitative yields. The simple experimental procedure along with easy recovery and reusability of the catalyst has led to development of a clean and environmentally friendly approach for the synthesis of  $\alpha$ -amino nitriles.

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## 1. Introduction

The Strecker reaction, which affords  $\alpha$ -amino nitriles by condensation of an aldehyde, NH<sub>3</sub>, and KCN, was first reported in 1850. It has received great interest as the oldest and most viable multi-component reaction (MCR) in organic synthesis due to the C–C bond formation and rich chemistry of the nitrile functional group.<sup>1</sup> For example, subsequent hydrolysis of  $\alpha$ -amino nitriles is the most straightforward route for the synthesis of  $\alpha$ -amino acids on both lab and technical scale even after 160 years of the initial introduction of the Strecker reaction.  $\alpha$ -Amino acids are themselves key precursors for the synthesis of proteins and have several applications as chiral building blocks in the pharmaceutical industry.<sup>2</sup> For instance, saframycin A shows potential anti-tumor activity.<sup>3</sup> Furthermore,  $\alpha$ -amino nitriles are versatile intermediates for the preparation of 1,2-diamines, and nitrogen or sulfur-containing heterocycles such as imidazoles and thiadiazoles.<sup>4,5</sup>

$\alpha$ -Amino nitriles are generally prepared by the nucleophilic addition of the cyanide anion to an imine formed in situ (classical Strecker reaction)<sup>6</sup> or preformed (modified Strecker reaction).<sup>7</sup> A number of alternative cyanide sources have been introduced to overcome problems associated with KCN. Examples include

Bu<sub>3</sub>SnCN,<sup>8a</sup> Et<sub>2</sub>AlCN,<sup>8b</sup> (EtO)<sub>2</sub>P(O)CN,<sup>8c</sup> EtOCO CN,<sup>8d</sup> (CH<sub>3</sub>)<sub>2</sub>C(OH)CN,<sup>8e</sup> and K<sub>2</sub>[Fe(CN)<sub>6</sub>],<sup>9</sup> which are often hazardous, toxic, and require harsh reaction conditions. However, trimethylsilyl cyanide (TMSCN) is a promising alternative, due to its nature as an effective, easily-handled, and relatively safe cyanation reagent for the nucleophilic addition to imines<sup>10</sup> and carbonyl double bonds.<sup>11</sup> It is noteworthy that TMSCN is able to transfer the cyanide ion only in the presence of a catalyst. Therefore, the Strecker reaction has been promoted by a variety of Lewis or Bronsted acid catalysts such as, Fe(Cp)<sub>2</sub>PF<sub>6</sub>,<sup>12a</sup> InI<sub>3</sub>,<sup>12b</sup> RhI<sub>3</sub>,<sup>12c</sup> Cu(OTf)<sub>2</sub>,<sup>12d</sup> I<sub>2</sub>,<sup>12e</sup> BiCl<sub>3</sub>,<sup>12f</sup> La(N-O<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O, GdCl<sub>3</sub>·6H<sub>2</sub>O,<sup>12g</sup> NiCl<sub>2</sub>,<sup>12h</sup> Ga(OTf)<sub>3</sub>,<sup>12i</sup> GaCl<sub>3</sub>,<sup>12j</sup> CeCl<sub>3</sub>,<sup>12k</sup> Pr(OTf)<sub>3</sub>,<sup>12l</sup> RuCl<sub>3</sub>,<sup>12m</sup> FeCl<sub>3</sub>,<sup>12n</sup> and *p*-toluenesulfonic acid.<sup>12o</sup> These catalysts all homogeneously catalyze the Strecker reaction. However, conventional homogeneous catalysts show many limitations such as the use of expensive or toxic catalytic systems, difficulty in separation, tedious work-up and waste discarding.<sup>12</sup> Hence, the tendency toward heterogeneous catalysts is of great importance due to straightforward separation, waste reduction, and simple recovery and reuse. Heterogeneous conditions have been reported for some simple catalysts including guanidine HCl,<sup>13a</sup> LiClO<sub>4</sub>,<sup>13b</sup> Fe(ClO<sub>4</sub>)<sub>3</sub>,<sup>13c</sup> and Zr(HSO<sub>4</sub>)<sub>4</sub>.<sup>13d</sup> However, incorporation of active catalyst species into an organic or inorganic polymer framework demonstrates special advantages: additional reactants activation by support, high surface area, lower contamination of products; and possibility to apply continuous flow versus batch configuration on large scales.<sup>14</sup>

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