

Catalyst-free multicomponent Strecker reaction in acetonitrile

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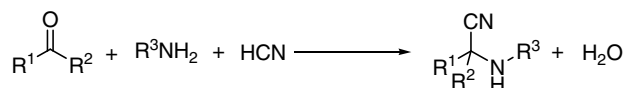
Abstract—The multicomponent Strecker reaction using trimethylsilyl cyanide was accomplished without any type of Lewis acid. The reaction performed in acetonitrile as solvent gave excellent results for any class of aldehydes (aromatic or aliphatic), as well as amines (aromatic or aliphatic). In many cases, α -aminonitrile product was isolated pure after the usual work-up, with quantitative chemical yields. A comparison between different solvents indicated that acetonitrile is the best choice. The rate comparison using different Lewis acids showed that all of them catalyzed the reaction in a similar extent, the difference with the acid Lewis-free being minimal.

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The Strecker reaction, discovered in 1850,¹ has been recognized as the first multicomponent reaction² published ever and has a central importance to the life sciences.³ The three-component coupling of an amine, a carbonyl compound (generally an aldehyde) and either hydrogen cyanide or its alkaline metal cyanides to give α -aminonitriles⁴ constitutes an important indirect route in the synthesis of α -amino acids⁵ (Scheme 1).

There is a one-pot sequential version of the Strecker multicomponent reaction, which should not be considered a proper multicomponent reaction, because it implies two sequential additions: first, the addition of the carbonyl compound and the amine to form the corresponding imine and then the addition of the alkaline metal cyanide for trapping the in situ formed imine. Anyhow, the Strecker reaction has been amply used in the synthesis of many natural products.⁶

One of the initial drawbacks of this reaction is the use of highly toxic cyanide derivatives. In order to avoid



Scheme 1.

Keywords: Multicomponent reactions; Strecker reaction; Aminonitriles; Aldehydes; Amines.

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partially this inconvenience, the use of trimethylsilyl cyanide has been introduced. In this way, the usual solvent used (water) could be changed for typical organic solvents (toluene, methylene chloride, acetonitrile, etc.), improving the solubility of the organic reagents as well as the reaction conditions. However, this new protocol involves the use of strong Lewis acid, blossoming many of them, such as lithium perchlorate,⁷ polymeric scandium triflamide,⁸ vanadyl triflate,⁹ nickel(II) chloride,¹⁰ zinc halides,¹¹ ruthenium(III) chloride,¹² praseodymium triflate,¹³ ytterbium triflate¹⁴ and bismuth(III) chloride,¹⁵ even montmorillonite KSF¹⁶ or iodine.¹⁷ In some cases, the protocols require tedious work-up leading to the generation of large amount of waste. Moreover, some of the Lewis acids used are toxic¹⁸ as well as their hydrolysis products. Therefore, there is a further scope to explore milder, safer and more efficient protocols for this reaction.

There are a couple of papers, which attracted our attention on the possibility to overcome the use of acid Lewis catalysts. In the first one, which is not properly a multicomponent reaction, the reaction was performed in the absence of solvents and heating the mixture at 100 °C, with the consequent problems associated for the stability of the reagents and products.¹⁹ In the second one, the reaction was performed with expensive ionic liquids.²⁰

These two papers remarked the great impact of a solvent on the reaction, and, therefore we commenced our study by measuring this effect. We chose the reaction of 4-chlorobenzaldehyde, aniline and trimethylsilyl cyanide

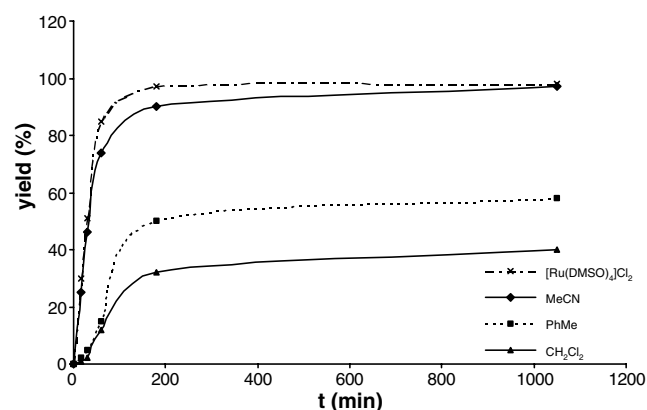
Table 1. Multicomponent Strecker reaction

$$\text{R}^1\text{CHO} + \text{R}^2\text{NH}_2 + \text{Me}_3\text{SiCN} \xrightarrow[25\text{ }^\circ\text{C}]{\text{MeCN}} \text{R}^1\text{CH}(\text{CN})\text{NHR}^2$$

Entry	α -Aminonitrile			
	No.	R ¹	R ²	% Yield ^a
1	1	4-ClC ₆ H ₄	Ph	97
2	2	Ph	Ph	92
3	3	Pr ⁱ	Ph	85
4	4	Ph	4-ClC ₆ H ₄	53
5	5	<i>c</i> -C ₆ H ₁₁	4-ClC ₆ H ₄	70
6	6	4-ClC ₆ H ₄	4-MeC ₆ H ₄	92
7	7	Ph	4-MeC ₆ H ₄	78
8	8	4-ClC ₆ H ₄	PhCH ₂	>99
9	9	2-Furyl	PhCH ₂	>99
10	10	Pr ⁱ	PhCH ₂	85
11	11	<i>n</i> -C ₅ H ₁₂	PhCH ₂	98
12	12	Ph	Bu ⁿ	75

^a Isolated yields of pure product after work-up or column chromatography (silica gel; hexane/ethyl acetate).

in a 1:1:1 molar ratio, as a model to give the corresponding α -aminonitrile **1** (Table 1). Initially we carried out four parallel reactions and we took out aliquots at 15, 30 min, 1, 3 and 17.5 h. These aliquots were hydrolyzed and GC-analyzed using 1,3,5-trimethylbenzene as internal standard for the yield calculations (Fig. 1), the yields being calculated for the final α -aminonitrile product and corroborated with the remaining starting amine and aldehyde, when possible (no formation of the imine derivative). Thus, when the reaction was performed in methylene chloride as solvent the yield was very low, 40% after 18 h (12% after 1 h), and the analysis of different aliquots over the time showed that after 3 h the reaction did not change practically (32% yield), keeping the same ratio of starting materials and products (a small and constant amount of the corresponding imine was detected). When the reaction was performed in toluene, the shape of the reaction rate was similar giving a slightly better yield, 58% after 18 h (15% after 1 h). However, in this case after 3 h the yield (50%) did not increase so much, the aldehyde and amine were totally consumed to form the corresponding imine. Surprisingly, when the reaction was

**Figure 1.**

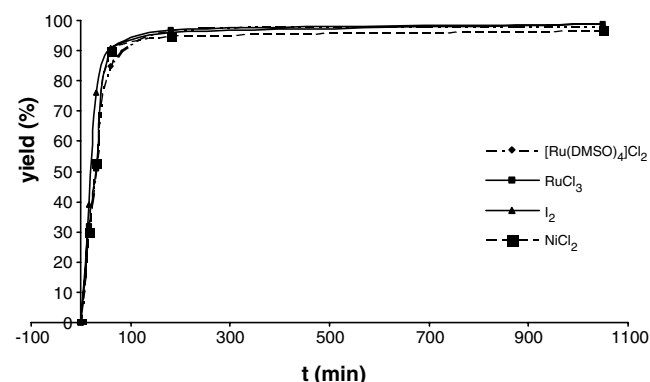
performed using acetonitrile, the rate was quite faster, giving the expected α -aminonitrile **1** in excellent 97% yield (74% and 90% yield after 1 and 3 h, respectively). In addition, the product was obtained pure after the normal work-up.

Once we found acetonitrile as the best solvent for the multicomponent Strecker reaction using trimethylsilyl cyanide, we measured the impact on the reaction rate of the Lewis acid catalyst [Ru(DMSO)₄]Cl₂,²¹ and the difference was minimal when the reaction was carried out using 5 mol % of this complex, obtaining 85% and 97% yield of product **1** after 1 and 3 h, respectively (Fig. 1).

After testing the low impact of [Ru(DMSO)₄]Cl₂ on the standard model reaction, we tested other typical catalysts previously used for this multicomponent reaction, such as NiCl₂, I₂ and RuCl₃ (anhydrous) and, in our hands, the four catalysts gave similar results (Fig. 2). Thus, when the reaction was performed using 5 mol % of NiCl₂, the yields were 90% and 95%, 91% and 96% for I₂, and 90% and 97% for RuCl₃, respectively, after 1 and 3 h. It should be noticed that at low reaction times (15 min) the yields were 25%, 30%, 30%, 32% and 39% for the uncatalyzed reaction, and using [Ru(DMSO)₄]Cl₂, NiCl₂, RuCl₃ and I₂ catalyzed reactions, respectively, so confirming the minimal role of the catalyst under this protocol reaction.

Once we found that the impact of some Lewis acid on the multicomponent Strecker reaction in acetonitrile was nearly superfluous and its presence could be avoided, we studied the scope of this protocol using acetonitrile as solvent and the reaction was quenched after 17.5 h at room temperature (Table 1).

These multicomponent coupling reactions proceed very efficiently at ambient temperature with high selectivity and giving in some cases the expected α -aminonitrile pure just after the normal work-up,²² as is the case of compounds **1**, **8**, **9** and **11**. In all cases, no cyanohydrin trimethylsilyl ethers were detected by GC–MS analyses. This method gave good results independently of the nature of the starting aldehyde (aliphatic or aromatic), the

**Figure 2.**

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