



Rhodium(III) iodide hydrate catalyzed three-component coupling reaction: synthesis of α -aminonitriles from aldehydes, amines, and trimethylsilyl cyanide

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ABSTRACT

Aryl imines formed from aldehydes and amines undergo smoothly in situ nucleophilic addition with trimethylsilyl cyanide (TMSCN) in the presence of catalytic amount of hydrated rhodium(III) iodide to afford the corresponding α -aminonitriles in excellent yield. The low catalytic loading (2 mol %), mild experimental conditions, and short reaction time (mostly within 13 min) represent the key features of this novel catalytic system.

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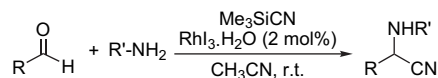
1. Introduction

The Strecker reaction is one of the most efficient and straightforward methods for the synthesis of α -aminonitriles,¹ which are very useful precursors for the synthesis of α -amino acids and various nitrogen containing heterocycles such as imidazoles and thiadiazoles, etc.² α -Amino acids are in turn of great biological and economical importance due to their significance in chemistry and biology, and are useful as chiral building blocks.³ The classical Strecker reaction is generally carried out by the nucleophilic addition of cyanide ion to the imines using different Lewis acid or Lewis base catalysts.⁴ Subsequently, several modifications of the Strecker reaction have been reported using a variety of cyanating agents such as α -trimethylsilyloxynitriles and diethylphosphorocyanidate under various reaction conditions.⁵ The use of TMSCN is a safer and more effective cyanide anion source for the nucleophilic addition reactions compared to hydrogen cyanide, sodium cyanide, or potassium cyanide.

Recently, numerous methods have also been developed for the synthesis of α -aminonitriles from aldehydes, amines, and TMSCN or tributyltin cyanide catalyzed by various Lewis acids such as lithium perchlorate, polymeric scandium triflamide, vanadyl triflate, NiCl₂, BiCl₃, zinc halides, RuCl₃, ytterbium triflate, montmorillonite, iodine, and La(NO₃)₃·6H₂O or GdCl₃·6H₂O, etc.⁶ There are also a few

reports using without catalyst.⁷ But their reaction time lies in the range of hours. Solid catalysts such as heteropoly acids⁸ and guanidine hydrochloride⁹ have been employed for the synthesis of α -aminonitriles. Most recently, a method utilizing 5 mol % Fe(Cp)₂PF₆ was reported for the synthesis of α -aminonitriles of ketones and aldehydes.¹⁰ However, many methods involve the use of strong acidic conditions, extended reaction time, and tedious work up leading to the generation of a large amount of toxic waste. Therefore, there is a need of an efficient method for the synthesis of α -aminonitriles in terms of shorter reaction time and in excellent yield.

In light of our success in developing several catalytic systems for the synthesis of chiral¹¹ and achiral cyanosilylether,¹² we extend them to the Strecker reaction. We wish to herein report a simple method for the synthesis of α -aminonitriles in the presence of a catalytic amount (2 mol %) of rhodium(III) iodide hydrate in acetonitrile at rt (Scheme 1).



Scheme 1.

2. Results and discussions

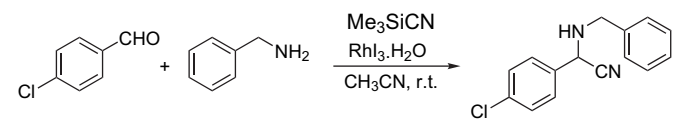
The Strecker reaction of 4-chlorobenzaldehyde, benzyl amine, and TMSCN in various solvents is examined in the presence of

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catalytic amount of rhodium(III) iodide hydrate at rt. As shown in Table 1, 1 mol% $\text{RhI}_3 \cdot \text{H}_2\text{O}$ gives α -aminonitriles with 85% yield in 10 min in CH_3CN (entry 2), while decreasing the catalyst loading up to 0.5 mol% it gives lower yield of 70% in 10 min (entry 1). With 2 mol% catalyst the yield is increased that affords the corresponding 2-(benzylamino)-2-(4-chlorophenyl)acetone nitrile in 99% yield within 10 min (entry 3). $\text{RhI}_3 \cdot \text{H}_2\text{O}$ (5 mol%) also gives 99% yield in 10 min. The solvents examined were dichloromethane, chloroform, benzene, tetrahydrofuran, and acetonitrile. Among these solvents tested, acetonitrile is shown to be the best (Table 1). Accordingly, 2 mol% $\text{RhI}_3 \cdot \text{H}_2\text{O}$ catalyst loading in CH_3CN as a solvent is considered optimal for the synthesis of α -aminonitriles.

A variety of aldehydes including aromatic, aliphatic as well as α,β -unsaturated ones and different amines were coupled with TMSCN under these conditions at rt (Table 2). Only 50–60% reaction conversion was observed without catalyst in acetonitrile at rt even after 1 h. The reaction of benzaldehyde with benzyl amine or aniline is completed within 10 min with 97 and 95% yield, respectively (entries 1 and 2). Similar reaction of benzaldehyde with *p*-methyl benzyl amine takes place in 12 min with 95% yield (entry 3). The *p*-methoxybenzaldehyde or *p*-tolualdehyde with benzyl amine also proceeds nicely within 12 min with 92 and 93% yield, respectively (entries 5 and 6). Benzaldehyde or 4-chlorobenzaldehyde reacts with cyclohexylamine to give 'relatively' reduced yield of the products (entries 4 and 9). 4-Methoxy benzyl amine, 4-chlorobenzaldehyde, and TMSCN give 97% yield in 10 min (entry 10). The reaction of 3-fluoro or 3-phenoxy benzaldehyde with benzyl amine produces the corresponding products in excellent yield of 98 and 99% in 10 and 12 min, respectively (entries 11 and 13). *m*-Phenoxybenzaldehyde reacts with aniline or *p*-methyl benzyl amine so as to give 96% yield within 10 min (entries 12 and 14). It should be noted that the reaction of 4-nitrobenzaldehyde and benzyl amine gave no reaction product at all. This indicates that strongly electron-withdrawing substituent such as *p*-nitro may not induce the Strecker reaction (entry 15). α,β -Unsaturated cinnamaldehyde offers 99% yield of the corresponding aminocyno compound in 8 min (entry 16), whereas hydrocinnamaldehyde produces 91% yield in 12 min (entry 17). The reaction of hexanal and heptaldehyde gives the corresponding products in 88 and 91% yield, respectively (entries 18 and 19). This indicates that aliphatic aldehydes entail 'comparatively' lower yield with 'longer' reaction time (20 min). 2-Furaldehyde (entries 20 and 21) creates the corresponding aminonitrile compound in good yield again in longer reaction time (18 and 25 min). The acid sensitive

Table 1
Three-component synthesis of α -aminonitriles under various conditions^a



Entry	Catalyst (mol %)	Time (min)	Yield ^b (%)
1	0.5	10	70
2	1.0	10	85
3	2.0	10	99
4	5.0	10	99
5	2.0	15	92 ^c
6	2.0	15	86 ^d
7	2.0	25	90 ^e
8	2.0	30	66 ^f

^a $\text{RhI}_3 \cdot \text{H}_2\text{O}$ was added to a mixture of 1 mmol of benzaldehyde, 1 mmol of benzyl amine, and 1.2 mmol of TMSCN.

^b Isolated yield.

^c In the presence of CH_2Cl_2 .

^d In the presence of CHCl_3 .

^e In the presence of THF.

^f In the presence of benzene.

aldehydes such as 2-furaldehyde and cinnamaldehyde both form the aminocyno compound in good yield. This may indicate that the catalytic system selectively activates the carbonyl function and keeps the furan ring and double bond of cinnamaldehyde intact.

This method requires no additives to promote the reaction. No cyanohydrin trimethylsilyl ethers (an adduct between aldehyde and trimethylsilylcyanide) were obtained under these reaction conditions probably because of the rapid formation of the imine intermediate by rhodium(III) iodide hydrate. It is noteworthy that when carrying out the reaction with acetophenone, 65% of Strecker product and 30% cyanohydrin trimethylsilyl ethers are obtained. This means that ketones undergo mixed reactions of both Strecker reaction and cyanosilylation. The imine prepared from acetophenone and benzylamine undergoes reaction in the presence of 2 mol% $\text{RhI}_3 \cdot \text{H}_2\text{O}$ with TMSCN to give 70% α -aminonitriles in 1 h. The reaction of ammonia as an amine source with acetophenone yields no product of α -aminonitriles in presence of 2 mol% $\text{RhI}_3 \cdot \text{H}_2\text{O}$ even after 2 h. Instead 60% cyanosilylation product was isolated after overnight stirring. In contrast to our reaction time and low catalyst loading (2 mol%), 5–10 h is required in the presence of 10 mol% of BiCl_3 .^{6c} With montmorillonite KSF clay as a catalyst,⁶ⁱ 3.0–5.5 h is consumed for completion of the reaction in the presence of 1.0 g clay; 1–8 h of reaction time and 20 mol% I_2 ^{6j} is necessary for completion of the reaction. Recently, a method utilizing 5 mol% $\text{Fe}(\text{Cp})_2\text{PF}_6$ is reported where 20 min is needed for the synthesis of α -aminonitriles.¹⁰ From these result, it is evident that 2 mol% $\text{RhI}_3 \cdot \text{H}_2\text{O}$ is a very efficient catalyst in terms of reaction time and yield for the synthesis of α -aminonitriles.

3. Summary

In conclusion, we have described a very simple, convenient, and practical method for the synthesis of α -aminonitriles through three-component coupling reaction of aldehydes, amines, and TMSCN using rhodium(III) iodide hydrate. The reaction with acetophenone gives 65% of Strecker product and 30% of cyanohydrin trimethylsilyl ether. The major advantage of this method is that operational simplicity at rt within a short reaction time and low catalyst loading (2 mol%). This reaction may require the shortest reaction time and the lowest catalyst quantity of all the previous studies in recent years. Excellent yield is obtained for both aromatic and aliphatic aldehydes. Studies concerning the asymmetric reaction as well as the application of the rhodium(III) iodide hydrate in the synthesis of chiral α -aminonitriles are in progress.

4. Experimental section

4.1. General

In all cases the ¹H NMR (200 MHz) spectra were recorded with Varian Gemini 2000 spectrometer. Chemical shifts are reported in parts per million in CDCl_3 with tetramethylsilane as internal standard. ¹³C NMR data were collected on a Varian Gemini 2000 spectrometer (100 MHz). GC–MS were recorded with 1200L Single Quadrupole GC/MS System with 3800GC/Varian.

All the chemicals were purchased from Aldrich and Fluka. Solvents were obtained from commercial sources and purified using standard methods if necessary. Flash chromatography silica gel (230–400 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated Silica gel 60-F₂₅₄ plates.

4.2. General procedure for the synthesis of α -aminonitriles

To a mixture of aldehyde (1 mmol) and amine (1 mmol) in acetonitrile (1 ml) were added TMSCN (1.2 mmol) and rhodium(III)

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