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Supramolecular Catalysis of Strecker Reaction in Water under Neutral Conditions in the Presence of β-Cyclodextrin†

K. Surendra, N. Srilakshmi Krishnaveni, A. Mahesh, and K. Rama Rao*

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India

drkrrao@yahoo.com

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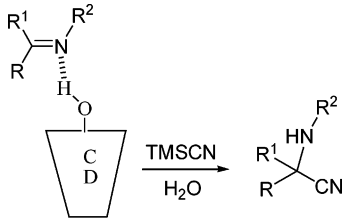

An environmentally benign and highly efficient procedure for the nucleophilic addition of trimethylsilyl cyanide to imines (Strecker reaction) has been developed under biomimetic conditions in water in the presence of β-cyclodextrin to afford α-aminonitriles in quantitative yields. The use of cyclodextrin precludes the use of either acid or base, and the catalyst can be recycled a number of times without loss in activity.

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 thiadiazoles, imidazoles, etc.[2] α-Amino acids are also of great biological and economical importance due to their significance in chemistry and biology and as useful chiral building blocks.[3] The classical Strecker reaction is generally carried out by the nucleophilic addition of cynide ion to the imines using different Lewis acid or base catalysts.[4] Subsequently, several modifications of the Strecker reaction have been reported using a variety of cyanating agents such as α-trimethylsiloxynitriles or diethylphosphorocyanidate under various reaction conditions.[5] However, trimethylsilyl cyanide is a safe and easy to handle reagent and more effective cyanide ion source for the nucleophilic addition reactions under mild conditions as compared to hydrogen, sodium, or potassium cyanides.

Although nucleophilic addition reaction to imines is a great source for the synthesis of a variety of amines,[6] the activation of the C═N bond, which is generally poor in reactivity, is necessary to obtain satisfactory efficiencies. Such activation can be classified as either post- or preactivation. In the case of postactivation, the C═N bond is not substituted with an activating group, and therefore, a Bronsted or Lewis acid or a metallic species is essential to effectively activate the formation of iminium cations or the equivalent species.[7] On the other hand, in the case of preactivation, the C═N bond is substituted with an activating group, such as carbonyl, sulfonyl, sulfinyl, phosphoryl, or silyl, to facilitate the addition reaction.[8]

Recently, one-pot procedures have also been developed for the synthesis of α-aminonitriles from aldehydes, amines, and trimethylsilyl cyanide or tributyltin cyanide using different Lewis acids such as lithium perchlorate, polymeric scandium triflamide, vanadyl triflate, $NiCl_2$, $BiCl_3$, zinc halides, $RuCl_3$, ytterbium triflate, and montmorillonite, etc.[9] However, most of these methods involve the use of strong acidic conditions, expensive reagents, extended reaction times, harsh conditions, and tedious workup leading to the generation of a large amount of toxic waste. Furthermore, many of these protocols are limited to aldehydes only and are not applicable to ketones.

There is also a recent report of carrying out these reactions in ionic liquids,[10] water-containing DMF,[4d] and $Sc(OTf)_3$ in water.[11] These ionic liquids have been shown to have serious drawbacks, especially imidazoliums with PF_6 and BF_4 anions that are as toxic as benzene on certain aquatic ecosystems and also liberate hazardous HF during recycling.[12] Apart from this, the high cost[13] and disposability of these solvents also limit their utility. Moreover, these reactions were unsuccessful in water

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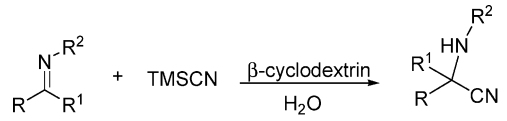
SCHEME 1



R = aryl, naphthyl; R^1 = H, CH_3; R^2 = aryl, benzyl, tosyl

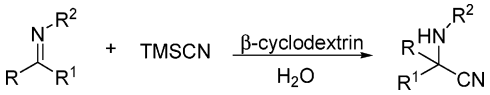
alone. To the best of our knowledge, efficient carbon−carbon bond formation via nucleophilic attack of cynide anion to the imines without pre- or postactivation has yet to be reported in water without using any acid or base catalyst.

With green chemistry becoming a central issue in both academic and industrial research in the 21st century,[14] the development of environmentally benign and clean synthetic procedures has become the goal of present day organic synthesis. Thus, there is a need for developing nucleophilic addition of cyanide anion to the imines (Strecker reaction) in water with a recyclable catalyst and without the use of any harmful organic solvents because water is a safe, economical, and environmentally benign solvent.[15] To achieve these ideal conditions, the best choice appeared to be through supramolecular catalysis involving cyclodextrins with water as a solvent.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host−guest complexes by noncovalent bonding as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, mimicking of biochemical selectivity, which is due to orientation of the substrate by complex formation positioning only certain regions for favorable attack, will be superior to chemical selectivity, which involves random attack due to intrinsic reactivity of the substrate at different regions. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins[16] prompted us to attempt the Strecker reaction of various aldimines and ketoimines under biomimetic conditions using cyclodextrins with water as solvent at room temperature (Scheme 1).

This is the first practically feasible Strecker reaction of various aldimines and ketoimines with trimethylsilyl cyanide in water. The reaction proceeds efficiently at room temperature without the need of any acid or base catalyst. The reaction goes to completion in a short time (1−2 h) (Table 1). This methodology is compatible with various substituted aldimines and ketoimines such as chloro, bromo, fluoro, methyl, methoxy, allyloxy, nitro, and double bonds under mild reaction conditions. No byproduct formation was observed. All of the products were characterized by mass, ^{1}H NMR, and IR spectroscopy and compared with the known compounds.[9] Moreover, these reactions are clean with nearly quantitative yields as compared to conventional methods, with shorter reaction times, higher selectivities, and recyclable catalyst. All of the reactions do take place with α-CD; however, *β*-CD was chosen as the catalyst since it is inexpensive and easily accessible. Though asymmetric induction was seen to some extent in these reactions, the ee's observed are not encouraging (<10%). However, when these reactions are carried out in the presence of sugars such as glucose and sucrose, the yields are only to the extent of 30% even after 12 h. These experiments indicate the substantial role of cyclodextrin. Thus, cyclodextrin may be forming a reversible complex with the imine, thus facilitating the reaction with the cyanide ion in its microenvironment.

TABLE 1. ***β*-Cyclodextrin-Catalyzed Strecher Synthesis of α-Amino Nitriles in Water**



entry	R	R^1	R^2	time (h)	yield[a] (%)
1	C_6H_5	H	C_6H_5	1.0	98[b]
2	C_6H_5	H	4-F-C_6H_4	1.0	98
3	C_6H_5	H	2-CH_3-C_6H_4	1.0	96
4	C_6H_5	H	2-OCH_3-C_6H_4	1.0	95
5	C_6H_5	H	C_6H_5-CH_2	1.5	92
6	4-Br-C_6H_4	H	C_6H_5	1.0	98
7	4-Cl-C_6H_4	H	4-F-C_6H_4	1.0	98
8	4-Me-C_6H_4	H	C_6H_5	1.0	96
9	4-Me-C_6H_4	H	Ts	1.0	94
10	2,4,6-tri-Me-C_6H_2	H	C_6H_5	1.0	94
11	4-MeO-C_6H_4	H	C_6H_5	1.0	96
12	2,4-di-MeO-C_6H_3	H	C_6H_5	1.0	94
13	4-allyloxy-C_6H_4	H	C_6H_5	1.0	95
14	4-NO_2-C_6H_4	H	C_6H_5	2.0	90
15	C_6H_5-CH=CH	H	C_6H_5	2.0	90
16	1-naphthyl	H	4-F-C_6H_4	1.0	92
17	2-naphthyl	H	C_6H_5	1.0	95
18	$C_{10}H_{20}$	H	C_6H_5	2.0	90
19	C_6H_5	CH_3	C_6H_5	2.0	94
20	4-Me-C_6H_4	CH_3	C_6H_5	2.0	94
21	2-naphthyl	CH_3	C_6H_5	2.0	92
22	C_6H_{10}	CH_3	C_6H_5	2.0	90

[a] Isolated yields. [b] Catalyst was recovered and resued for five consecutive runs in this reaction without change in the yield and purity.

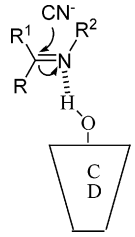


FIGURE 1. *β*-CD catalysis of the Strecher reaction.

The catalytic activity of cyclodextrins for this Strecker reaction is established by the fact that no reaction was observed in the absence of cyclodextrin. The mechanism of Strecker reaction was postulated as follows: hydrogen bonding of CD hydroxyl with the nitrogen of the imine increases the electrophilicity of the imine carbon, thus activating it for attack by the cyanide ion (Figure 1).

These CD-mediated water solvent reactions are very useful both from economical and environmental points of view.

(13) Ionic Liquids cost 60−400 USD/50 g as opposed to *β*-CD, which costs 105 USD/100 g.

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β-Cyclodextrin, apart from being nontoxic is also considered as metabolically safe.[17] In contrast to the existing methods using many acidic catalysts, this methodology is very simple, high yielding, and environmentally friendly. Significant improvements offered by this procedure are (i) faster reaction times, (ii) operationally simple and mild conditions (room temperature), (iii) excellent yields, (iv) cost efficiency providing recyclability of the catalyst, and (v) green aspect avoiding hazardous organic solvents and toxic and expensive reagents. Further potential applications of this reaction are under study.

Experimental Section

General Procedure. To β-CD (0.1 mmol) dissolved in water (10 mL) was added imine (1 mmol) in methanol (1 mL) followed by trimethylsilyl cyanide (1 mmol) and the mixture stirred at room temperature until the reaction was complete (Table 1). The organic material was extracted with ethyl acetate, dried, and concentrated under reduced pressure, and the resulting product, though seen as single compound by TLC, was further purified by passing over a column of silica gel. After extraction with ethyl acetate, the aqueous phase was lyophilized to get the CD.

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Supporting Information Available: General information and experimental data for the compounds described in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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