Quantitative Synthesis of α-Amino Nitriles through Strecker Reaction of Aldimines with TMSCN Catalyzed by Tetrabutylammonium phthalimide-*N*-oxyl

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Abstract: Tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO) was used as an efficient organocatalyst to catalyze the Strecker reaction of diverse aldimines with trimethylsilyl cyanide (TMSCN) in EtOH. The reaction proceeded smoothly at room temperature to afford the corresponding α-aminonitriles in quantitative yields under mild reaction conditions**.**

Keywords: α-Amino Nitriles; Strecker Reaction; Aldimines; Nucleophilic Organocatalysis; Tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO); TMSCN.

Introduction

α-Aminonitriles are important synthetic intermediates for preparing of α-amino acids and Nitrogen-containing heterocycles [1]. The Strecker reaction, nucleophilic addition of cyanide ion to the imines, is of great importance to modern organic chemistry as it offers one of the most direct and viable methods for the synthesis of α-amino nitriles [2]. Some of the Strecker methodologies rely on the use of toxic cyanide derivatives involving harsh reaction conditions, which encompasses their individual problems, particularly when large-scale applications are considered. In order to avoid partially this inconvenience, acetone cyanohydrin, diethylaluminium cyanide, trimethylsilyl cyanide (TMSCN), etc. have been introduced as cyanide sources in the Strecker reaction [3]. TMSCN is known to be easy to handle and more effective cyanide ion source for the nucleophilic addition under mild conditions as compared to HCN, NaCN or KCN.

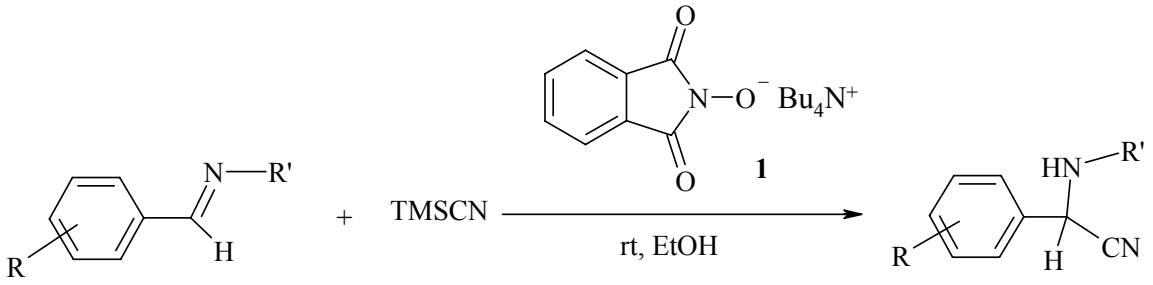
Both homogeneous and heterogeneous catalysts have been used for the synthesis of α-aminonitriles. The Strecker reaction has been catalyzed by using various promising Lewis acidic, Lewis basic and metal complexes catalytic systems. Among different Lewis basic catalytic systems, stable *N*-heterocyclic carbenes (NHCs), *N*-oxides, quaternary ammonium halides, tertiary amines, are worthwhile to be mentioned [4]. Therefore, development of new catalysts which operate under milder conditions is a challenge attracting much attention.

Recently, we have introduced phthalimide-*N*-oxyl (PINO) anion as a novel nucleophilic catalyst for cyanosilylation of carbonyl compounds [5-6], protection of alcohols and phenols by hexamethyldisilazane (HMDS) [7] and cyclotrimerization of isocyanates [8,9]. In continuation of our interest to develop the catalytic scope of the PINO nucleophile, we herein wish to report tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO, **1**) as an efficient organocatalyst for the quantitative Strecker reaction of diverse aldimines with TMSCN.

Results and Discussion

At first place, 4-chlorobenzaldimine **2a** was used as a model compound and the effect of different solvents such as CH_2Cl_2 and EtOH on the reaction time and obtained yield was investigated by using 1.2 equivalent of TMSCN in the presence of different catalyst loading

TBAPINO **1** (1-3 mol%) at room temperature (**Scheme 1**). The progress of the reaction was easily monitored by TLC.



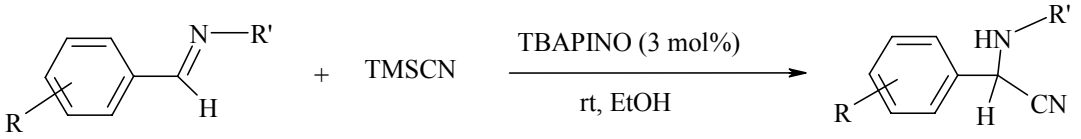
2a-f **3a-f**

R= Cl, NO2, Me, OMe, OH
R'= *p*-Tolyl, Benzyl

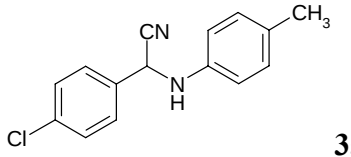
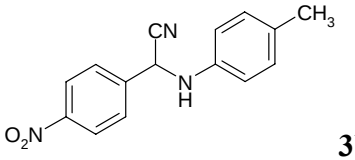
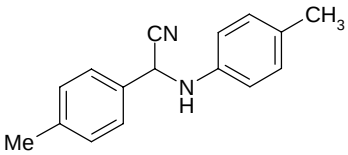
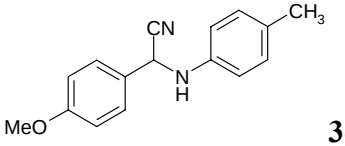
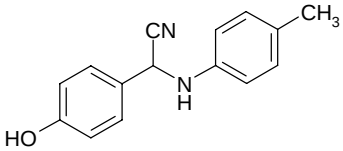
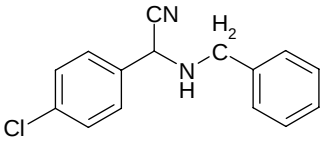
Scheme 1. Strecker reaction of different aldimines catalyzed by TBAPINO.

CH_2Cl_2 required long reaction time and afforded moderate yields. However, by switching the solvent to EtOH, a quantitative yield of the desired α-aminonitriles (**3a**) was obtained (Entry 1, **Table 1**). The optimal reaction conditions (TBAPINO, 3 mol%; EtOH) was developed to other aldimines bearing both electron-withdrawing and electron-donating groups or different amine counterpart (Entries 2-6, **Table 1**). Interestingly, the products of the Strecker reaction are insoluble in EtOH and this allowed the convenient separation of the catalyst from products. On the other hand, data in Table 1 show that the nature of substituents on the aromatic ring of corresponding benzaldehyde derivatives has a great effect on the required reaction time for completion. In general, aldimines bearing electron-withdrawing groups (entries 1,2,6) react faster than those with electron-donating groups (entries 3,4,5).

Table 1. Strecker Reaction of different Aldimines Catalyzed by TBAPINO at Room Temperature



2 **3**

Entry	R	Time (h)	Product (3)	Conversion (%)
1	Cl	2.5	 **3a**	100
2	NO_2	2	 **3b**	100
3	Me	4	 **3c**	100
4	OMe	3.5	 **3d**	100
5	OH	4	 **3e**	100
6	Cl	2.5	 **3f**	100

Conclusion

In conclusion, we have described an efficient and general method for the quantitative synthesis of α-aminonitriles using aldimines and TMSCN catalyzed by tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO) as a metal-free organocatlyst at ambient temperature. By using TBAPINO catalyst, the efficiency of the Strecker reaction of diverse aldiminies has been improved considerably and work up is easy.

Experimental

Typical Procedure for the Synthesis of α-Aminonitriles

TMSCN (1.2 mmol, 0.15 mL) was added to a solution of 1.0 mmol of an appropriate aldimine and TBAPINO (0.03 mmol, 12 mg) in EtOH (2.5 mL). The mixture was stirred at room temperature for the indicated time in Table 1. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was filtered on a Büchner funnel to afford the desired products (**3a-f**) as solids in pure form.

Acknowledgment

The partial financial support of this work by The Research Council of Iran University of Science and Technology (IUST), Iran is gratefully acknowledged.

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