

KHSO₄-catalyzed Three-component Synthesis of α -Aminonitriles

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ABSTRACT

A simple, convenient and general method has been developed for the synthesis of α -aminonitriles by a one-pot three-component condensation of aldehydes, amines and trimethyl silyl cyanide under solvent-free conditions in the presence of a catalytic amount of KHSO₄ in good yields. The new method compares well in terms of yields with alternative methods. In general the reaction times are much shorter and the work up much easier.

KEYWORDS

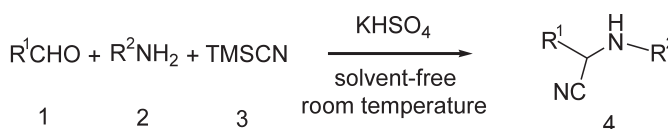
One-pot, KHSO₄, trimethyl silyl cyanide, α -aminonitriles.

1. Introduction

α -Aminonitriles are versatile precursors for the synthesis of α -aminoacids,¹ various nitrogen- and sulphur-containing heterocycles such as imidazoles, thiadiazoles² and pharmaceuticals.³ The Strecker reaction, nucleophilic addition of a cyanide ion to 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 -aminonitriles.⁴ The Strecker reaction between an aldehyde, an amine and hydrogen cyanide is widely regarded as the first multicomponent reaction.¹ Its reliability, the ready availability of the starting materials and the versatility of the resulting products make it a very important process for the large-scale production of aminoacids, herbicides and chelating agents. The classical Strecker reaction is usually carried out in an aqueous solution and the work-up procedure is tedious. Thus several modifications to the Strecker reaction have been reported using a variety of cyanide reagents,⁵ such as diethyl phosphorocyanidate and α -trimethylsiloxy nitriles but the use of trimethylsilyl cyanide (TMSCN) is a safer and more effective cyanide anion source for the nucleophilic addition reactions of imines under mild conditions.⁶ The Strecker reaction has been studied extensively by using various promising Lewis acids,⁷ Lewis base catalysts,⁸ metal complexes and metal-salen complexes.⁹ In recent years, a number of highly effective catalysts have been successfully used for asymmetric Strecker reactions, such as Lipton's cyclic dipeptide,^{10a} Corey's cyclic guanidine,^{10b} Jacobsen's Schiff base^{10c,d} and Feng's N,N-dioxide.^{10e} Strecker methodologies for the synthesis of α -aminonitriles have been reported in ionic liquids and water instead of regular organic solvents.^{7,11}

However, many of these methods involve the use of expensive reagents, harsh conditions, extended reaction times, and also require tedious workup, leading to the generation of a large amount of toxic waste. Furthermore many of these catalysts are deactivated or sometimes decomposed by amines and water that exist during imine formation. In order to overcome these problems, recently one-pot procedures have been developed for this transformation.¹² In continuation of our work to develop new catalysts for organic transformations,¹³ here we report a mild, efficient and environmentally benign method for the

preparation of α -aminonitriles from aldehydes, amines and trimethylsilyl cyanide in the presence of KHSO₄ as a safe catalyst under solvent-free conditions at room temperature (Scheme 1).



Scheme 1

2. Results and Discussion

In recent years the use of inorganic reagents in solvent-free conditions has rapidly increased, as these reactions often need milder reaction conditions, easier work-up and provide higher selectivity than similar reactions using organic reagents in solution.^{14,15}

KHSO₄ is one of the components of a triple salt with formula 2KHSO₅·KHSO₄·K₂SO₄, a so-called oxone which is used as a highly efficient, mild oxidizing agent in many organic reagents.¹⁶ Very recently, we have reported the use of KHSO₄ as an efficient catalyst for the synthesis of 1,1-diacetates under solvent-free conditions.¹⁷ Then, we decided to prepare α -aminonitriles by using KHSO₄ as an efficient catalyst at room temperature under solvent-free conditions. In a typical general procedure, a mixture of aldehyde, amine and trimethylsilyl cyanide under solvent-free conditions was stirred in the presence of KHSO₄ (no reaction was observed in the absence of catalyst). The reaction proceeded smoothly at room temperature to afford the corresponding α -aminonitrile in high yields (95 %). Similarly, a variety of aldehydes were coupled with a range of amines and trimethylsilyl cyanide in a one-pot operation by using this procedure to produce α -aminonitriles in 92–97 % yields, as shown in Table 1. This method is equally effective with aldehydes bearing electron-withdrawing substituents in the aromatic ring. This method does not require any additives or stringent reaction conditions to proceed. The reaction conditions are mild enough to perform these reactions in the presence of either acid- or base-sensitive substrates.

The amount of catalyst has been optimized to 5 mmol %; however, lesser amounts (3 mmol %) also work with longer reaction

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Table 1 Synthesis of α -aminonitriles in the presence of KHSO_4 as a catalyst.

Entry	1	2	Product	Time/min	Yield/% ^a
1	benzaldehyde	aniline	4a	10	95
2	benzaldehyde	benzyl amine	4b	10	93
3	4-methoxy benzaldehyde	aniline	4c	10	94
4	4-methoxy benzaldehyde	benzyl amine	4d	10	93
5	4-methyl benzaldehyde	aniline	4e	10	95
6	4-methyl benzaldehyde	benzyl amine	4f	10	92
7	4-chloro benzaldehyde	aniline	4g	8	97
8	4-chloro benzaldehyde	benzyl amine	4h	8	95

^a Yields of isolated products.

times. Furthermore, ketones did not yield any products under these reaction conditions. The reactions are clean and highly selective, affording exclusively α -aminonitriles in high yields in short reaction times. No undesired side products (such as cyanohydrin trimethylsilyl ether, an adduct between the aldehyde and trimethylsilyl cyanide) were observed because of the rapid formation of the imine intermediate. The insolubility of KHSO_4 in different organic solvents provides an easy method for separation of the catalyst and the product. The catalyst was separated by filtration and reused after activation with only a gradual decrease in activity observed. For example, the reaction of benzaldehyde, aniline and trimethylsilyl cyanide gave the corresponding α -aminonitrile (4a) in 95 %, 92 % and 90 % yields over three cycles.

The synthesis of α -aminonitriles was carried out using various common solvents such as CCl_4 , acetonitrile, methanol, ethyl acetate and THF. Using KHSO_4 as a catalyst, the highest yield of products was obtained under solvent-free conditions. In addition, the time required for completion of the reaction was found to be less when no solvent was used.

To show the merits and advantages of using KHSO_4 as a catalyst, our method is compared with reported reactions (see Table 2).

In conclusion, the present procedure using KHSO_4 provides an efficient synthesis of α -aminonitriles by a one-pot three-component system of aldehydes, amines and TMSCN . The simple experimental conditions and product isolation procedures combined with easy recovery and reuse of the catalyst are expected to contribute to the development of clean and environmentally friendly strategies for the synthesis of α -aminonitriles. The salient features of this methodology are: general applicability to different types of aldehydes and amines, using cheap and commercially available reagents, the low cost of the catalyst, solvent-free conditions, low toxicity of the catalyst, short reaction times, simple experimental procedures, recyclability of the catalyst and high yields of products. Finally this report provides environmentally benign chemical processes.

Table 2 Synthesis of α -aminonitrile (4a) with KHSO_4 and comparison of the result with other reported methods.

Entry	Catalyst	Time/min	Yield/%	References
1	LiClO_4	1440	96	18
2	$\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$	60	96	19
3	I_2 (10 mol %)	60	94	20
4	KSF (10 g)	210	90	21
5	InCl_3 (30 mol %)	360	75	22
6	RuCl_3 (20 mol %)	1200	74	23
7	GuHCl (3 mol %)	60	94	24
8	cellulose sulphuric acid	45	97	25
9	KHSO_4	10	95	this work

3. Experimental

All chemicals were obtained from Merck (Darmstadt, Germany) and used as received. All products were characterized by melting point, IR, ^1H NMR and GC/MS analysis. Melting points (uncorrected) were measured using Electrothermal IA 9100 digital melting point apparatus (Tehran, Iran). ^1H NMR spectra were recorded on a Bruker AQS AVANCE 300 MHz spectrometer (Tehran, Iran) (CDCl_3 solution) using TMS as an internal standard. IR spectra were recorded on KBr disks using a Bruker Tensor 27 FT-IR spectrometer (Tehran, Iran). Yields were based on GC/mass analysis using an Agilent (Denver, CO, USA) 6890 GC system (HP-5 capillary 30 mm $\times$ 320 μm $\times$ 0.25 μm nominal).

3.1. General Procedure for the Synthesis of α -Aminonitriles

A mixture of aldehyde (1 mmol), amine (1 mmol), trimethylsilyl cyanide (1 mmol) and KHSO_4 (5 mol %) was stirred vigorously at room temperature for the indicated time (see Table 1). The progress of the reaction was monitored by TLC using ethyl acetate:n-hexane (1:3) as eluent ($R_f = 53\%$). The reaction mixture was extracted with dichloromethane (3 $\times$ 10 mL) and the solvent was evaporated. The residue was recrystallized from ethanol to give pure product.

3.2. Selected Physical Data

4a. M.p. 73–74 $^\circ\text{C}$, IR (KBr) ν_{max} : 3360, 3025, 2950, 2230, 1600, 1500, 1460, 1315, 1140, 995, 750 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 4.1 (br s, 1H, NH), 5.4 (s, 1H), 6.5–6.8 (m, 5H), 7.1–7.8 ppm (m, 5H). GC/MS: 208 (M^+).

4b. Colourless oil, IR (KBr) ν_{max} : 3400, 2930, 2230, 1650, 1514, 1400, 1108, 1028, 920, 825, 751 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 1.80 (brs, 1H, NH), 3.90 (AB q, 2H, $J = 13.0$ Hz), 4.85 (s, 1H), 6.85 (d, 1H, $J = 8.0$ Hz), 7.15 (t, 1H, $J = 7.8$ Hz), 7.25–7.40 (m, 6H), 7.45–7.51 ppm (m, 2H). GC/MS: 222 (M^+).

4c. M.p. 94–95 $^\circ\text{C}$, IR (KBr) ν_{max} : 3380, 3060, 2930, 2240, 1600, 1500, 1455, 1290, 1116, 1040, 929, 760 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 3.80 (s, 3H), 4.1 (d, 1H, $J = 8.1$ Hz), 5.30 (d, 1H, $J = 8.1$ Hz), 6.50 (d, 2H, $J = 8.0$ Hz), 6.80 (t, 1H, $J = 7.9$ Hz), 7.05 (d, 2H, $J = 8.0$ Hz), 7.25 (t, 2H, $J = 7.9$ Hz), 7.50 (d, 2H, $J = 8.0$ Hz). GC/MS: 238 (M^+).

Acknowledgements

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