

Zr(HSO₄)₄ Catalyzed One-Pot Strecker Synthesis of α -Amino Nitriles from Aldehydes and Ketones under Solvent-Free Conditions

A.R. Hajipour^{a,b,*}, Y. Ghayeb^b and N. Sheikhan^b

^aDept. of Pharmacology, University of Wisconsin, Medical School, 1300 University Avenue, Madison, 53706-1532, WI, USA

^bPharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran

(Received 16 May 2009, Accepted 26 July 2009)

A mild and efficient method has been developed for the preparation of α -amino nitriles from the condensation of aldehydes and ketones with aniline and TMSCN in the presence of a catalytic amount of Zr(HSO₄)₄ under solvent-free conditions at room temperature.

Keywords: Strecker, α -Amino nitriles, Zr(HSO₄)₄, Solid acid

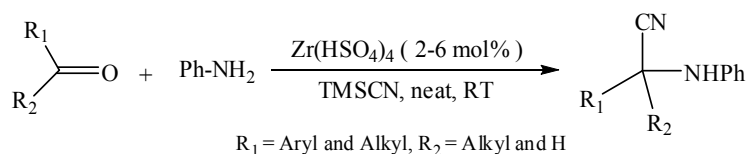
INTRODUCTION

One-pot multi-component condensation reactions are important and attractive due to the formation of multi-bonds in one pot, high atom economy, mild and simplified conditions and environmentally benign friendliness. Strecker reaction as the first multicomponent reaction (MCR), which was discovered in 1850, represented one of the most important reactions, especially from the life science viewpoint [1]. In this reaction three components including a carbonyl compound (generally an aldehyde), an amine and either alkaline metal cyanide or hydrogen cyanide couple together and produce α -amino nitriles. The Strecker reaction is one of the most straightforward and efficient methods for the synthesis of α -amino nitriles as one of the very useful synthones for the preparation of α -amino acids [2] and heterocyclic compounds such as imidazoles and other biologically important molecules [3]. α -Amino acids have the great biological and economical

significance because of their widespread use in chemistry and biology. For example, they are the key precursors for the synthesis of proteins and have several applications as the chiral building blocks in the pharmaceutical industry [4]. Generally, α -amino nitriles are prepared by the nucleophilic addition of cyanide ion to the imines (*in situ* generated from condensation of aldehydes with amines) in the presence of Lewis acid or Lewis base catalysts. Many cyanide sources such as HCN [5], KCN [6], Bu₃SnCN [7], Et₂AlCN [8], (Et₂O)P(O)CN [9] and TMSCN [10] have been used for Strecker reaction. Among the aforementioned reagents, TMSCN is the safer and more efficient cyanide anion source [11].

Many Lewis acid catalysts including NiCl₂ [12], Cu(OTf)₂ [13], RuCl₃ [14], iodine [15], La(NO₃)₃.6H₂O or GdCl₃.6H₂O [16], InCl₃ [17], RhI₃.H₂O [18] and Fe(CP)₂PF₆ [19] have recently been employed for the preparation of α -amino nitriles from aldehydes, amines and trimethylsilylcyanide or tributyltin cyanide. Solid catalysts such as montmorillonite KSF [20], silica-supported heteropoly acids [21], Guanidine

*Corresponding author. E-mail: haji@cc.iut.ac.ir



Scheme 1

hydrochloride [22] and cellulose sulfuric acid [23] have been used for the synthesis of α -amino nitriles from aldehydes. The synthesis of α -amino nitriles from ketones has been reported under different conditions [24-26].

Recently, the solvent-free reactions have attracted great interest due to the pollution reducing, low cost and convenient and straightforward work-up. In continuation of our efforts to develop new methods in organic synthesis [27-29], we found out that zirconium hydrogen sulfate has many advantages over sulfuric acid alone. This reagent is safe and environmentally benign and presents fewer disposal problems. Lately, the use of $\text{Zr(HSO}_4)_4$ as an efficient catalyst for the preparation of acylals, regeneration of carbonyl compounds by cleavage of C=N bonds and acetylation or formylation of primary, secondary and tertiary alcohols has been published [30-33]. Herein, we wish to report an efficient method for one-pot three-component synthesis of α -amino nitriles from various carbonyl compounds, aniline and TMSCN in the presence of catalytic amount of $\text{Zr(HSO}_4)_4$ under solvent-free conditions at room temperature (Scheme 1).

EXPERIMENTAL

General

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. $\text{Zr(HSO}_4)_4$ was synthesised according to the reported procedure [31]. Products were characterized by spectroscopy data (IR, ^1H NMR, ^{13}C NMR spectra) and elemental analyses and melting points. ^1H NMR (400, 500 MHz) and ^{13}C NMR (125 MHz) spectra were run in CDCl_3 solution relative to TMS (0.00 ppm). IR spectra were recorded on a Shimadzu 435 IR spectrophotometer and performed using KBr pellets. All melting points were taken on a Gallenkamp melting apparatus and were uncorrected.

General Procedure for the Preparation of α -Amino Nitriles

A mixture of carbonyl compound (1 mmol), aniline or other amines (1 mmol), trimethylsilylcyanide (1.2 mmol) and zirconium hydrogen sulfate (0.02-0.04 mmol for aldehydes and 0.06 mmol for ketones) was stirred at room temperature. The completion of the reaction was monitored with TLC (ethyl acetate/cyclohexane, 1/3), then water (10 ml) was added and the reaction mixture was extracted by ethyl acetate (10×3 ml), washed with brine and dried over anhydrous MgSO_4 . Solvent evaporated under reduced pressure and the product was purified by column chromatography using silica gel to afford the pure product. The spectral (IR, ^1H NMR and ^{13}C NMR) data and the elemental analyses of the products are given below. Spectral data were compared with the literature data. Entries 6, 14 and 17 are new compounds.

2-Anilino-2-phenyl acetonitrile (entry 1): IR (KBr): 3337, 2237 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.84 (d, 1H, $J = 8.0$ Hz), 5.25 (d, 1H, $J = 8.4$ Hz), 6.60 (d, 2H, $J = 8.0$ Hz), 6.72 (t, 1H, $J = 8.0$ Hz), 7.04-7.11 (m, 2H), 7.27-7.31 (m, 3H), 7.41-7.43 (m, 2H).

2-Anilino-2-(4-methoxy phenyl) acetonitrile (entry 2): IR (KBr): 3328, 2227 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.65 (s, 3H), 3.78 (bs, 1H), 5.15 (d, 1H, $J = 6.4$ Hz), 6.59 (d, 2H, $J = 8.0$ Hz), 6.69-6.79 (m, 3H), 7.09 (d, 2H, $J = 8.0$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz).

2-Anilino-2-(2-chloro phenyl) acetonitrile (entry 3): IR (KBr): 3338, 2241 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.83 (d, 1H, $J = 7.6$ Hz), 5.54 (d, 1H, $J = 8.0$ Hz), 6.60 (d, 2H, $J = 8.0$ Hz), 6.72 (t, 1H, $J = 7.6$ Hz), 7.09 (t, 2H, $J = 8.0$ Hz), 7.20-7.22 (m, 2H), 7.29-7.31 (m, 1H), 7.55-7.58 (m, 1H).

2-Anilino-2-(4-methyl phenyl) acetonitrile (entry 4): IR (KBr): 3309, 2243 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 2.21 (s, 3H), 3.83 (bs, 1H), 5.20 (s, 1H), 6.59 (d, 2H, $J = 8.0$ Hz), 6.71 (t, 1H, $J = 7.2$ Hz), 7.07-7.11 (m, 4H), 7.29 (d, 2H, $J =$

7.6 Hz).

2-Anilino-2-(4-chloro phenyl) acetonitrile (entry 5): IR (KBr): 3301, 2246 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.84 (bs, 1H), 5.24 (d, 1H, J = 6.0 Hz), 6.56 (d, 2H, J = 7.8 Hz), 6.73 (t, 1H, J = 7.2 Hz), 7.09 (t, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.4 Hz).

2-Anilino-2-(2,6-dichloro phenyl) acetonitrile (entry 6): IR (KBr): 3407, 2245 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.53 (d, 1H, J = 10.0 Hz), 6.09 (d, 1H, J = 10.4 Hz), 6.66 (d, 2H, J = 8.0 Hz), 6.72 (t, 1H, J = 7.2 Hz), 7.07-7.14 (m, 3H), 7.21 (d, 2H, J = 7.6 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 46.21, 115.32, 116.94, 121.28, 129.99, 130.08, 130.46, 131.61, 135.55, 144.45; Anal. Calcd. for C₁₄H₁₀N₂Cl₂: C, 60.67; H, 3.64; N, 10.11; Found: C, 60.10; H, 3.80; N, 10.20.

2-Anilino-2-(3-methoxy phenyl) acetonitrile (entry 7): IR (KBr): 3354, 2225 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.65 (s, 3H), 3.86 (bs, 1H), 5.21 (s, 1H), 6.59 (d, 2H, J = 8.0 Hz), 6.72 (t, 1H, J = 7.6 Hz), 6.76 (dd, 1H, J = 2.0, 8.2 Hz), 6.93 (s, 1H), 6.98 (d, 1H, J = 7.6 Hz), 7.09 (t, 2H, J = 8.0 Hz), 7.19 (t, 1H, J = 8.0 Hz).

2-Anilino-2-(4-cyano phenyl) acetonitrile (entry 8): IR (KBr): 3354, 2237 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.19 (bs, 1H), 5.58 (s, 1H), 6.80 (d, 2H, J = 7.8 Hz), 6.99 (t, 1H, J = 7.4 Hz), 7.33 (t, 2H, J = 7.6 Hz), 7.81 (s, 4H).

2-Anilino-2-[4-(1-Anilino-1-cyano)-methyl] phenyl acetonitrile (entry 9): IR (KBr): 3330, 2238 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 2.22 (s, 1H), 5.54 (s, 1H), 6.83 (d, 2H, J = 7.7 Hz), 6.98 (t, 1H, J = 7.5 Hz), 7.34 (t, 2H, J = 8.0 Hz), 7.77 (s, 2H).

(E)-2-Anilino-4-phenyl 3-butenenitrile (entry 10): IR (KBr): 3351, 2224 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.92 (d, 1H, J = 9.6 Hz), 5.08-5.11 (m, 1H), 6.31 (dd, 1H, J = 4.8, 15.8 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.93 (t, 1H, J = 8.0 Hz), 7.08 (d, 1H, J = 16.0 Hz), 7.30-7.47 (m, 7H).

2-Anilino-2-furfuryl acetonitrile (entry 11): IR (KBr): 3375, 2242 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.21 (bs, 1H), 5.55 (d, 1H, J = 6.7 Hz), 6.48 (t, 1H, J = 2.6 Hz), 6.64 (d, 1H, J = 3.4 Hz), 6.84 (d, 2H, J = 7.8 Hz), 6.97 (t, 1H, J = 7.4 Hz), 7.33 (t, 2H, J = 7.8 Hz), 7.54 (d, 1H, J = 1.0 Hz).

2-Anilino-2-(5-methyl furfuryl) acetonitrile (entry 12): IR (KBr): 3330, 2241 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.14 (s, 3H) 3.95 (d, 1H, J = 8.0 Hz), 5.23 (d, 1H, J = 8.4 Hz), 5.81 (d, 1H, J = 2.0 Hz), 6.27 (d, 1H, J = 2.8 Hz), 6.58 (d, 2H, J =

8.0 Hz), 6.73 (t, 1H, J = 7.2 Hz), 7.09 (t, 2H, J = 8.8 Hz).

2-Anilino-2-phenyl propanenitrile (entry 13): IR (KBr): 3386, 2226 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.76 (s, 3H) 4.10 (s, 1H), 6.35 (d, 2H, J = 8.0 Hz), 6.61 (t, 1H, J = 8.0 Hz), 6.93 (t, 2H, J = 8.0 Hz), 7.16-7.23 (m, 3H), 7.44 (d, 2H, J = 7.2 Hz).

2-Anilino-2-(3-methoxy phenyl) propanenitrile (entry 14): IR (KBr): 3384, 2230 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.99 (s, 3H) 3.85 (s, 3H), 4.30 (bs, 1H), 6.61 (d, 2H, J = 8.0 Hz), 6.86 (t, 1H, J = 7.3 Hz), 6.93 (dd, 1H, J = 2.6, 8.0 Hz), 7.17 (t, 2H, J = 8.0 Hz), 7.21 (t, 1H, J = 2.0 Hz), 7.27 (d, 1H, J = 7.8 Hz), 7.37 (t, 1H, J = 7.9 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 33.74, 55.77, 57.53, 111.16, 114.29, 116.21, 117.55, 120.47, 121.05, 129.44, 130.77, 142.08, 143.90, 160.73; Anal. Calcd. for C₁₆H₁₃N₂O: C, 77.09; H, 5.26; N, 11.24; Found: C, 77.30; H, 5.40; N, 10.90.

1-Anilino-1-cycloheptane carbonitrile (entry 15): IR (KBr): 3365, 2238 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.65-1.70 (m, 2H), 1.72-1.81 (m, 6H), 2.00-2.05 (m, 2H), 2.33-2.38 (m, 2H), 3.69 (bs, 1H), 6.92-6.95 (m, 3H), 7.29 (t, 2H, J = 8.2 Hz).

1-Anilino-1-cyclopentane carbonitrile (entry 16): IR (KBr): 3368, 2235 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.89-1.97 (m, 4H), 2.16-2.21 (m, 2H), 2.41-2.46 (m, 2H), 3.90 (bs, 1H), 6.87 (d, 2H, J = 7.8 Hz), 6.92 (t, 1H, J = 7.4 Hz), 7.28-7.31 (m, 3H).

5-Methoxy-1-anilino-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (entry 17): IR (KBr): 3395, 2227 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.59 (bs, 1H), 1.91-1.93 (m, 2H), 2.19-2.21 (m, 1H), 2.66-2.67 (m, 1H), 2.74-2.77 (m, 1H), 2.86-2.90 (m, 1H), 6.91-6.97 (m, 4H), 7.29 (t, 2H, J = 7.7 Hz), 7.34 (t, 1H, J = 8.0 Hz), 7.43 (d, 1H, J = 7.8 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 17.34, 22.87, 31.75, 55.47, 55.98, 110.62, 117.20, 120.70, 120.89, 122.38, 126.51, 127.98, 129.74, 135.85, 143.91, 157.64; Anal. Calcd. for C₁₈H₁₈N₂O: C, 77.67; H, 6.52; N, 10.06; Found: C, 77.50; H, 6.80; N, 9.80.

RESULTS AND DISCUSSION

In order to obtain the best reaction conditions, the reaction of benzaldehyde (1 mmol), aniline (1 mmol) and TMSCN (1.2 mmol) was examined in the presence of 4 mol% of Zr(HSO₄)₄ as catalyst in acetonitrile at room temperature. When the reaction mixture was stirred at room temperature for 6 h, some

Table 1. Effect of Different Amounts of the Catalyst on the Synthesis of 2-Anilino-2-phenyl Acetonitrile^a

Entry	1	2	3	4	5
Mol% catalyst	1	2	4	10	15
Time (min) ^b	10	5	5	10	30 ^c

^aBenzaldehyde (1 mmol), aniline (1 mmol), TMSCN (1.2 mmol) and Zr(HSO₄)₄ (1-15 mol%) under solvent-free conditions at room temperature. ^bThe time of completion of the reaction based on TLC. ^cThe reaction did not complete and undesired product was observed.

undesired products were observed. Therefore, we tried to trigger this reaction under solvent-free conditions and found that the reaction took place in 5 min. Optimized amounts of the catalyst were provided using several molar amounts of Zr(HSO₄)₄ under solvent-free conditions (Table 1). As it is shown in Table 1, no improvement was observed for the reaction rate by increasing the amount of the catalyst from 2 to 4 mol% (entries 2-3, Table 1). Both the lesser (1 mol %) and the higher (10 mol%) amounts of the catalyst worked with longer reaction times (entries 1 and 4, Table 1). The reaction did not complete even after 30 min and using 15 mol% of the

catalyst and undesired products were observed (entry 5, Table 1).

In order to show the catalytic activity of Zr(HSO₄)₄ in comparison to the other catalysts, we have compared the results of the synthesis of 2-anilino-2-phenyl acetonitrile from benzaldehyde, aniline and TMSCN at room temperature. The results are presented in (Table 2).

We employed 2-4 mol% of the catalyst for one-pot synthesis of α -amino nitriles from aldehydes under solvent-free conditions at room temperature (entries 1-13, Table 3). Aromatic, aliphatic and heterocyclic aldehydes under the optimum conditions coupled with aniline and TMSCN to produce the corresponding α -amino nitriles in high to excellent yields. The mildness of the reaction conditions permits furfural, 5-methyl furfural and cinnamaldehyde to undergo reactions successfully to produce α -amino nitriles in high yields and short reaction times without formation of any polymerization products (entries 10-12, Table 3). The reaction times for 2-chloro benzaldehyde and 2,6-dichloro benzaldehyde were longer than the others (entries 3 and 6, Table 3), which may be due to the steric hindrance effect. It should be noted that electron-withdrawing substituents such as -CN, or -Cl, decreased the Strecker reaction yields (entry 8, Table 3).

To the best of our knowledge, only few studies on Strecker

Table 2. Effect of Different Catalysts for Synthesis of α -Amino Nitriles from Benzaldehyde (1 mmol), Aniline (1 mmol) and TMSCN at Room Temperature and Different Solvents or Solvent-Free Conditions

Entry	Catalyst (mol%)	TMSCN (mmol)	Solvent	Time	Yield (%)	Ref.
1	Cu(OTf) ₂ (2)	TMSCN (1)	CH ₃ CN	6 h	89	[13]
2	GuHCl (3)	TMSCN (1.1)	CH ₃ OH	1 h	94	[22]
3	PW/SiO ₂ (7)	TMSCN (1.5)	CH ₃ CN	5 min	98	[21]
4	PW/SiO ₂ (7)	KCN (1.5)	CH ₃ CN	30 min	95	[21]
5	Cellulose sulfuric acid (0.05 g)	TMSCN (1.2)	CH ₃ CN	45 min	97	[23]
6	La(NO ₃).6H ₂ O (10)	TMSCN (1.2)	CH ₃ CN	1 h	96	[16]
7	GdCl ₃ .6H ₂ O (10)	TMSCN (1.2)	CH ₃ CN	1 h	94	[16]
8	InCl ₃ (30)	KCN (1.5)	THF	6 h	75	[17]
9	RhI ₃ .H ₂ O (2)	TMSCN (1.2)	CH ₃ CN	10 min	97	[18]
10	Fe(CP) ₂ PF ₆ (5)	TMSCN (1.3)	-	20 min	94	[19]
11	Catalyst-free	TMSCN (1.03)	CH ₃ CN	17.5 h	92	[34]
12	Zr(HSO ₄) ₄ (2)	TMSCN (1.2)	-	5 min	92	-

$\text{Zr}(\text{HSO}_4)_4$ Catalyzed One-Pot Strecker Synthesis of α -Amino Nitriles

Table 3. Strecker Synthesis of α -Amino Nitriles from Various Aldehydes and Ketones Catalyzed by $\text{Zr}(\text{HSO}_4)_4$ under Solvent-Free Conditions at Room Temperature

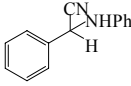
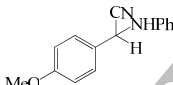
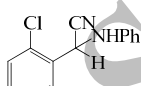
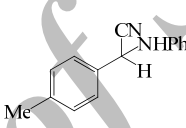
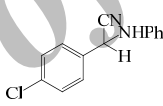
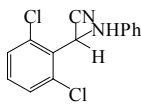
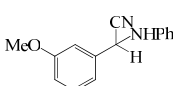
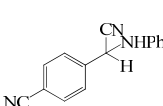
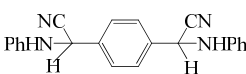
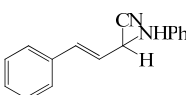
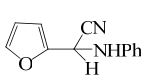
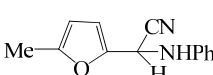
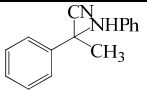
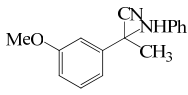
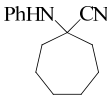
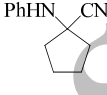
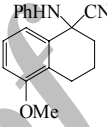
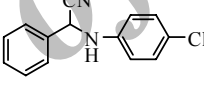
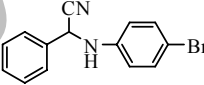
Entry	Substrate	Product	Time (min)	Yield (%) ^{a,b}	M.P.
1	Benzaldehyde		5	92	82-84
2	4-Methoxy benzaldehyde		10	85	94-97
3	2-Chloro benzaldehyde		30	80	63-66
4	4-Methyl benzaldehyde		10 ^b	90	72-74
5	4-Chloro benzaldehyde		10	85	104-106
6	2,6-Dichloro benzaldehyde		60	86	73-76
7	3-Methoxy benzaldehyde		15	91	56-58
8	4-Cyano benzaldehyde		15 ^c	70	118-121
9	Terephthalaldehyde		10 ^c	83	157-160
10	Cinnamaldehyde		15	85	104-106
11	Fufural		5	90	66-69
12	5-Methyl furfural		5	83	108-110

Table 3. Continued

13	Acetophenone		10	80	133-136
14	3'-Methoxy acetophenone		15	75	120-123
15	Cycloheptanone		20	90	83-86
16	Cyclopentanone		20	93	51-54
17	5-Methoxy-1-tetralone		20	84	99-102
18	Benzaldehyde ^d		10	85	69-72
19	Benzaldehyde ^f		10	88	94-96

^aIsolated yields. ^bThe products were characterized from their spectral (IR, ¹H NMR) and compared with authentic samples. ^c4 mol% catalyst. ^d4-chloro aniline was used. ^f4-Bromo aniline was used.

reaction with ketones have been reported in the literatures [19,24-26]. In this study, we examined the condensation of ketones with aniline and TMSCN in the presence of 6 mol% of Zr(HSO₄)₄ under solvent-free conditions at room temperature (entries 13-17, Table 3). The reactions proceeded in longer times in comparison to aldehydes, to produce the corresponding α -amino nitriles from ketones.

Furthermore, the reactions of benzaldehyde with other aromatic amines such as 4-chloro aniline and 4-bromo aniline in the presence of TMSCN as cyanating agent and Zr(HSO₄)₄ as catalyst were investigated. As it is displayed in Table 3 (entries 18-19), the corresponding α -amino nitriles were produced in high yields and short reaction times. Also, the reactions of benzaldehyde with TMSCN and aliphatic amines such as benzyl amine, homoveratryl amine and butyl amine in the presence of Zr(HSO₄)₄ as catalyst were examined under

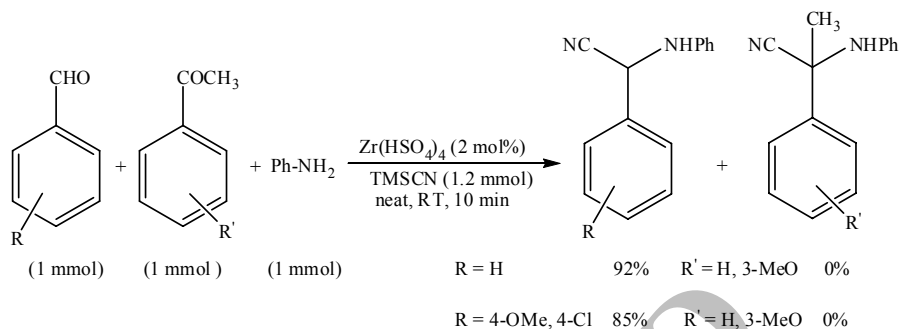
solvent-free conditions and room temperature. The yields of the corresponding α -amino nitriles after 3 h were low and the undesired products were observed. This may be due to the higher basicity of the aliphatic amines.

To measure the selectivity of this method, we started some competitive reactions for the preparation of α -amino nitriles from aldehydes in the presence of ketones using zirconium hydrogen sulfate as catalyst under solvent-free conditions. As shown in Scheme 2, the aldehydes in the presence of ketones were selectively converted to the corresponding α -amino nitriles and the starting ketones were recovered intact.

CONCLUSIONS

In conclusion, we have developed a facile, convenient and solvent-free method for the one-pot Strecker synthesis of α -

Zr(HSO₄)₄ Catalyzed One-Pot Strecker Synthesis of α -Amino Nitriles



Scheme 2

amino nitriles from the coupling of various aldehydes and ketones with aniline and trimethylsilyl cyanide using zirconium hydrogen sulfate as an efficient catalyst. Making use of inexpensive and relatively non-toxic catalyst, high catalytic efficiency, short reaction times, straightforward work-up and environmentally benign procedure are among the advantages of the method in question. Moreover, this method is highly selective for the preparation of α -amino nitriles from aldehydes in the presence of ketones. Therefore, this procedure is general and can be used for coupling of various aliphatic, aromatic, benzylic and cyclic aldehydes and ketones.

ACKNOWLEDGEMENTS

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran (A. R. H.) and Grants GM 033138, MH 065503, NS 033650 (A. E. R.) from the National Institute of Health. Further financial support from Center of Excellency in Sensor and Green Chemistry Research (IUT) and Isfahan Science & Technology Town (ISTT) is gratefully acknowledged.

REFERENCES

- [1] A. Strecker, *Ann. Chem. Pharm.* 75 (1850) 27.
- [2] Y.M. Shafran, V.A. Bakulev, V.S. Mokrushin, *Russ. Chem. Rev.* 58 (1989) 148.
- [3] a) L.M. Weinstock, P. Davis, B. Handelsman, R. Tull, *J. Org. Chem.* 32 (1967) 2823; b) W.L. Matier, D.A. Owens, W.T. Comer, D. Deitchman, H.C. Ferguson, R.J. Seidehamel, J.R. Young, *J. Med. Chem.* 16 (1973) 901; c) R.O. Duthaler, *Tetrahedron* 50 (1994) 1539.
- [4] a) D. Enders, J.P. Shilvock, *Chem. Soc. Rev.* 29 (2000) 359; b) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, 1999, p. 965; c) G. Dyker, *Angew. Chem. Int. Ed.* 36 (1997) 1700; d) J.A. Gonzalez-Vera, M.T. Garcia-Lopez, R. Herranz, *J. Org. Chem.* 70 (2005) 3660.
- [5] D. Enders, J.P. Shilvock, *Chem. Soc. Rev.* 29 (2000) 359.
- [6] S. Kobayashi, H. Ishitani, *Chem. Rev.* 99 (1999) 1069.
- [7] P. Vachal, E.N. Jacobsen, *J. Am. Chem. Soc.* 124 (2002) 10012.
- [8] S. Nakamura, N. Sato, M. Sugimoto, T. Toru, *Tetrahedron: Asymmetry* 15 (2004) 1513.
- [9] S. Harusawa, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* 20 (1979) 4664.
- [10] B.A. Bhanu Prasad, A. Bisai, V.K. Singh, *Tetrahedron Lett.* 45 (2004) 9565.
- [11] W.C. Groutas, D. Felker, *Synthesis* (1980) 861.
- [12] S.K. De, *J. Mol. Catal. A: Chem.* 225 (2005) 169.
- [13] S. Paraskar, A. Sudalai, *Tetrahedron Lett.* 47 (2006) 5759.
- [14] S.K. De, *Synth. Commun.* 35 (2005) 653.
- [15] L. Royer, S.K. De, R.A. Gibbs, *Tetrahedron Lett.* 46 (2005) 4595.
- [16] M. Narasimhulu, T.S. Reddy, K.C. Mahesh, S.M. Reddy, A.V. Reddy, Y. Venkateswarlu, *J. Mol. Catal. A: Chem.* 264 (2007) 288.
- [17] B.C. Ranu, S.S. Dey, A. Hajra, *Tetrahedron* 58 (2002) 2529.

- [18] A. Majhi, S.S. Kim, S.T. Kadam, *Tetrahedron* 64 (2008) 5509.
- [19] N.H. Khan, S. Agrawal, R.I. Kureshy, S.H.R. Abdi, S. Singh, E. Suresh, R.V. Jasra, *Tetrahedron Lett.* 49 (2008) 640.
- [20] J.S. Yadav, S.B.V. Reddy, B. Eeshwaraian, M. Srinivas, *Tetrahedron* 60 (2004) 1767.
- [21] E. Rafiee, S. Rashidzadeh, A. Azad, *J. Mol. Catal. A: Chem.* 261 (2007) 49.
- [22] H.A. Arefi, S. Khaksar, R.K. Shihoodi, *J. Mol. Catal. A: Chem.* 271 (2007) 142.
- [23] A. Shaabani, A. Maleki, *App. Catalysis A: General* 331 (2007) 149.
- [24] K. Matsumoto, J.C. Kim, N. Hayashi, G. Jenner, *Tetrahedron Lett.* 43 (2002) 9167.
- [25] G. Jenner, R.B. Salem, J.C. Kim, K. Matsumoto, *Tetrahedron Lett.* 44 (2003) 447.
- [26] G.K.S. Prakash, T. Mathew, C. Panja, S. Alconcel, H. Vaghoo, C. Do, G.A. Olah, *Proc. Natl. Acad. Sci. USA* 104 (2007) 3703.
- [27] A.R. Hajipour, A. Zarei, L. Khazdooz, B.B.F. Mirjalili, N. Sheikhan, S. Zahmatkesh, A.E. Ruoho, *Synthesis* 20 (2005) 3644.
- [28] a) A.R. Hajipour, M. Arbabian, A.E. Ruoho, *J. Org. Chem.* 67 (2002) 8622; b) A.R. Hajipour, B.B.F. Mirjalili, A. Zarei, L. Khazdooz, A.E. Ruoho, *Tetrahedron Lett.* 45 (2004) 6607.
- [29] A.R. Hajipour, B. Kooshki, A.E. Ruoho, *Tetrahedron Lett.* 46 (2005) 5503.
- [30] B.B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri, N. Sheikhan, *J. Chin. Chem. Soc.* 53 (2006) 95.
- [31] F. Shirini, M.A. Zolfigol, A. Safari, I. Mohammadpoor-Baltork, B.B.F. Mirjalili, *Tetrahedron Lett.* 44 (2003) 7463.
- [32] F. Shirini, M.A. Zolfigol, A. Safari, *J. Chem. Res. (S)* (2006) 154.
- [33] B.B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri, M.A. Karimi-Zarchi, Z. Zaghaghi, M. Parvaideh, *J. Iran. Chem. Soc.* 4 (2007) 340.
- [34] R. Martinez, D.J. Ramon, M. Yus, *Tetrahedron Lett.* 46 (2005) 8471.