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H_2SO_4/Silicagel: Highly Efficient Catalyst for the Synthesis of α-Aminonitriles Using Trimethysilyl Cyanide

Hossien A. Oskooie, Majid M. Heravi*, Akbar Sadnia, Fatemeh Jannati, and **Farahnaz K. Behbahani**

Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

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Summary. The multicomponent *Strecker* reaction using trimethylsilyl cyanide was performed at room temperature and α-aminonitriles were prepared in excellent yields in the presence of a catalytic amount of H_2SO_4 adsorbed on silica gel.

Keywords. Trimethylsilyl cyanide; α-Aminonitriles; H_2SO_4/silica gel; *Strecker* reaction; Multi component reactions.

Introduction

The *Strecker* reaction, discovered in 1850 [1], has been recognized as the first multicomponent reaction [2] published ever and has a central importance to the life sciences [3]. The three-component coupling of an amine, a carbonyl compound (generally an aldehyde), and either hydrogen cyanide or its alkaline metal cyanides to give α-aminonitriles [4] constitutes an important indirect route in the synthesis of α-amino acids [5, 6].

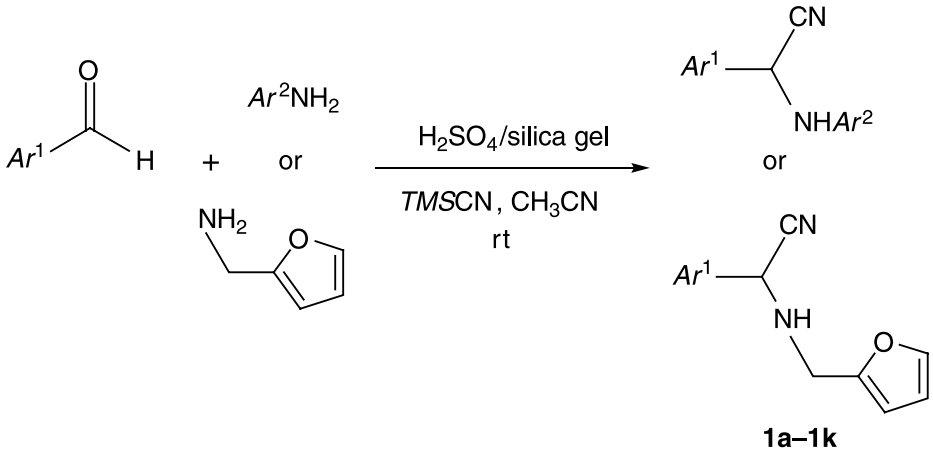
More recent protocols involve the use of strong *Lewis* acids, such as lithium perchlorate [7], polymeric scandium triflamide [8], vanadyl triflate [9], nickel(II) chloride [10], zinc halides [11], ruthenium(III) chloride [12], praseodymium triflate [13], ytterbium triflate [14], bismuth(III) chloride [15], montmorillonite KSF [16], iodine [17], $H_{14}[NaP_5W_{30}O_{110}]$ [18], and $Fe(ClO_4)_3$ [19]. However, in some cases, the protocols require tedious work-up leading to the generation of large amounts of waste. Moreover, some of the *Lewis* acids used as well as their hydrolysis products are toxic [20]. Therefore, there is a further scope to explore milder, safer, and more efficient protocols for this reaction. One of the initial drawbacks of this reaction is the use of highly toxic cyanide derivatives. In order to avoid partially this inconvenience, the use of trimethylsilyl cyanide (*TMS*CN) has been introduced. The synthetic utility of supported reagents has been demonstrated during the past ten years [21].

In recent years it has been shown that sulfuric acid adsorbed on silica gel can be used as a multipurpose acid catalyst [22]. In continuation of our interest performing reactions on solid supports [23], we now report in this paper the synthesis of α-aminonitriles using trimethylsilyl cyanide catalyzed by sulfuric acid adsorbed on silica gel as an easily available, inexpensive, and relatively green catalyst.

Results and Discussion

The reaction of aldehydes and amines with *TMS*CN in the presence of a catalytic amount of H_2SO_4/silicagel afforded the corresponding α-aminonitriles in acetonitrile as the solvent in high yields (Scheme 1, Table 1). The reaction is successful using amines with a variety of aldehydes, but not with ketones. These three-component coupling reactions proceeded efficiently at room temperature with high selectivity. No cyanohydrin trimethylsilyl ethers (an adduct be-

* Corresponding author. E-mail: mmh1331@yahoo.com



1a–1k

Ar^1: *Ph*, 4-Cl-*Ph*, 4-*Me*-*Ph*, 4-*Me*O-*Ph*, 4-*iPr*.-*Ph*, 4-NO_2-*Ph*; Ar^2: *Ph*, 4-Cl-*Ph*

Scheme 1

Table 1. H_2SO_4 adsorbed on silica gel catalyzed synthesis of α-aminonitriles using trimethylsilyl cyanide (*TMS*CN)

Entry	Aldehyde	Amine	Time/min	Product	mp/°C		Yield/%
					Observed	Ref.	
1	*Ph*–CHO	*Ph*–NH_2	60	**1a**	70–73	73–74 [9]	93
2	*Ph*–CHO	furfurylamine	65	**1b**	oil	yellow liq. [9]	98
3	Cl–*Ph*–CHO	*Ph*–NH_2	90	**1c**	105–108	109–112 [9]	96
4	Cl–*Ph*–CHO	furfurylamine	75	**1d**	oil	–	90
5	4-*Me*–Ph–CHO	*Ph*–NH_2	75	**1e**	74–76	76–78 [9]	90
6	4-*Me*O–*Ph*–CHO	*Ph*–NH_2	60	**1f**	92–96	94–95 [9]	92
7	4-*iPrPh*–CHO	*Ph*–NH_2	20	**1g**	63–72	–	90
8	4-*iPrPh*–CHO	4-Cl–*Ph*–NH_2	30	**1h**	80–86	–	30
9	4-*iPrPh*–CHO	furfurylamine	60	**1i**	oil	–	96
10	4-NO_2–*Ph*–CHO	4-Cl–*Ph*–NH_2	60	**1j**	oil	–	20
11	4-*Me*O–*Ph*–CHO	4-Cl–*Ph*–NH_2	90	**1k**	71–77	–	94

tween an aldehyde and *TMS*CN were obtained under these reaction conditions. This is due to the rapid formation and activation of the imines by H_2SO_4/silica gel. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields in a relatively short reaction time. This method is equally effective with aldehydes bearing electron withdrawing substituents in the aromatic ring.

In conclusion, we report a simple, convenient, and practical method for the synthesis of α-aminonitriles through a one-pot three-component coupling of aldehydes, amines, and *TMS*CN using H_2SO_4/silica gel as the catalyst. The major advantage of this method is that it is truly a one-pot procedure and that it does not require a separate step to prepare an imine for subsequent use. The significant features of this method include: operational simplicity, inexpensive reagents, no need for any additive to promote the reaction, high yields of products, and the use of relatively non-toxic reagents and solvents.

Experimental

General Procedure for the Preparation of α-Aminonitriles

A mixture of 1 mmol aldehyde, 1 mmol amine, 108 mg *TMS*CN (1.1 mmol), and 0.5 g H_2SO_4/silica gel in 5 cm^3 acetonitrile was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction, as monitored by TLC, the catalyst was recovered by filteration and 15 cm^3 of a 10% soln. of $NaHCO_3$ were added to the filtrate. Then the organic phase was separated and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the α-aminonitriles as crude products. Further purification by chromatography (eluent: petroleum ether/ethyl acetate) afforded α-aminonitriles in good yields (Table 1).

Adsorbtion of Sulfuric Acid on Silica Gel

A solution of 2 cm^3 conc. H_2SO_4 in 20 cm^3 acetone is added to a dispersion of 100 g silica gel (Merk 60, 70–230) in 200 cm^3

acetone and stirred at room temperature for 1 h. The solvent is removed under reduced pressure. A yellow–brown powder is obtained, which can be stored in a desiccator for long periods of times without any appreciable loss of activity.

2-(Furfurylamino)-2-(4-chlorophenyl)acetonitrile
(**1d**, $C_{13}H_{11}N_2ClO$)
IR (KBr): $\bar{\nu}_{max} = 3298, 2917, 2840, 2226, 1695, 1580, 1455, 1214, 1131, 1019, 960, 775\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 2.30$ (brs, 1H, NH), 4.0 (s, 2H), 5.08 (s, 1H), 6.40–6.60 (m, 2H), 6.75–6.90 (d, 2H), 7.40–7.60 (d, 2H) ppm.

2-(Phenylamino)-2-(4-isopropylphenyl)acetonitrile
(**1g**, $C_{17}H_{18}N_2$)
IR (KBr): $\bar{\nu}_{max} = 3332.0, 3025.13, 2953.0, 2223.52\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.18$ (d, 6H), 1.77 (m, 1H), 3.68 (d, 1H), 5.25 (d, 1H), 6.68 (d, 2H), 6.76 (t, 1H), 6.9 (d, 2H), 7.1 (d, 2H) ppm.

2-(4-Chlorophenylamino)-2-(phenyl)acetonitrile
(**1h**, $C_{14}H_{11}N_2Cl$)
IR (KBr): $\bar{\nu}_{max} = 3340.061, 3038.33, 2963.53, 2233.32\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.20$ (d, 6H), 1.80 (m, 1H), 3.70 (d, 1H), 5.38 (d, 1H), 6.78 (d, 2H), 6.85 (d, 1H), 7.10 (d, 2H), 7.5 (d, 2H) ppm.

2-(Furfurylamino)-2-(phenyl)acetonitrile (**1i**, $C_{13}H_{12}N_2O$)
IR (KBr): $\bar{\nu}_{max} = 3300, 2920, 2841, 2223, 1681, 1565, 1442, 1214, 1131, 1014, 910, 755\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.77$ (brs, 1H, NH), 3.9 (s, 2H), 4.0 (s, 1H), 6.15–6.35 (m, 2H), 7.0–7.25 (m, 4H) ppm.

2-(4-Chlorophenylamino)-2-(4-nitrophenyl)acetonitrile
(**1j**, $C_{15}H_{13}N_2ClO$)
IR (KBr): $\bar{\nu}_{max} = 3431, 2927, 2869, 2239, 1600, 1517\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 4.07$ (d, 1H), 5.39 (d, 1H), 6.70 (d, 2H), 6.90 (d, 2H), 7.20 (d, 2H), 7.47 (d, 2H), 7.9 (m, 2H) ppm.

2-(4-Chlorophenylamino)-2-(4-methoxyphenyl)acetonitrile
(**1k**, $C_{15}H_{13}N_2ClO$)
IR (KBr): $\bar{\nu}_{max} = 3380, 3053, 2922, 2241, 1601, 1500, 1451, 1295, 1117, 1041, 925, 762\,cm^{-1}$; H NMR ($CDCl_3$): $\delta = 3.80$ (s, 3H), 4.0 (d, 1H), 5.30 (d, 1H), 6.8 (d, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.50 (d, 2H) ppm; ^{13}C NMR (proton decoupled, $CDCl_3$): $\delta = 49.0$, 55.8, 113.5, 114.0, 117.9, 119.5, 126.3, 129.0, 129.8, 145.0, 160.1 ppm.

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