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A Novel and Efficient Method for the Synthesis of α–Aminonitriles by the Reaction of Aminals with Trimethylsilyl Cyanide Catalyzed by Iodine

M.R. Saidi* and N. Azizi
Depatment of Chemistry, Sharif University of Technologhy, P. O. Box 11365- 9516
Tehran, Iran

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Iodine, was found to be a practical and novel catalyst for the reaction of aminal and trimethylsilyl cyanide under mild and neutral reaction condition to afford the corresponding α-aminonitriles in high yields and short reaction times. Trimethylsilyl iodide derived *in situ* from elemental iodine and trimethylsillyl cyanide catalyzed this conversion.

Keywords: Trimethylsilyl cyanide, Carbonyl compounds, Iodine, Iminium salt, Aminal

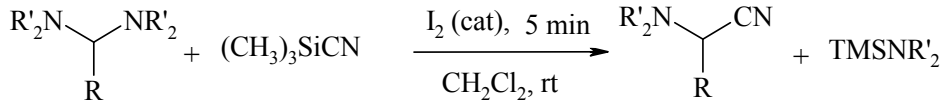
INTRODUCTION

The Mannich reaction provides an excellent method for carbon-carbon bond formation and its importance has been reflected in the ever-increasing number of suitable substrate and reaction conditions which have been developed in recent years [1]. Several important experimental modifications of Mannich reaction have been reported in the past decade, which involve the use of preformed iminium salts [2]. The preformed iminium salts can be prepared by a number of different methods, including the reaction of acetyl chloride with aminals [3], trifluroacetic anhydride with N-oxides [4], trichloromethylsilane with aminal and aminol ethers [5].

The Strecker reaction provides one of the most efficient methods for the synthesis of α-aminonitriles, which are useful intermediates in the synthesis of amino acids [6] and nitrogen containing heterocycles such as thiadiazoles, to give α-aminocarboxamides or are reduced to give 1,2-imidazoles, *etc.* with biological activities [7]. Moreover, among many other applications, they are readily hydrolyzed to diamines, which are of interest as ligands for platinum(II) complexes with potential antitumor properties [8-10].

The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution which have some limitations. Thus several modifications of the Strecker reaction have been reported using a variety of cyanating agent such as α-trimethylsiloxynitriles and diethyl phosphorocyanides under various reaction conditions [11]. Trimethylsilylcyanide (TMSCN) is a cyanide anion source provides promising and safer routes to these compounds [12]. Recently, one-pot procedures for the synthesis of α-aminonitriles from carbonyl compounds have also been developed in the presence of novel catalysts, using trimethylsilyl or tributyltin [13]. However, most of these reactions have long reaction time, tedious work up conditions and in some cases, a primary amines is needed as a source of imines. Thus the development of novel

* Corresponding author. E-mail*:* saidi@sharif.edu



Scheme 1

and practical method for the cyanation of iminiums under mild conditions has attracted much attention in organic synthesis.

Reaction of trimethylsilyl iodide, TMSI, with aminal produces iminium salts [14]. Although, TMSI can be prepared easily, but it is extremely sensitive to hydrolysis [15]. In continuation of our research work for *in situ* preparation of iminium salts [16] and with the aims of *in situ* generation of TMSI, herein we report the iodine-catalyzed cyanoamination of aminal by trimethylsilyl cyanide, TMSCN, to afford α–aminonitriles in high yields and very short time, Scheme 1. In the first step, we used catalytic amount of iodine at room temperature in a range of different solvents. Among the solvents examined (*i.e.*, acetonitrile, dichloromethane, acetone, toluene and petroleum ether), CH_2Cl_2 gave the best result. Optimum conditions found to be 0.2 equivalent (0.05 g) of iodine in CH_2Cl_2 as solvent. With these results in hand, addition of TMSCN in the present of catalytic amount of iodine to other aminals were studied using the optimal reaction conditions. A summary of the results is shown in Table 1. In all cases, a quantitative conversion of the aminals to the corresponding α-aminonitriles was observed. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields at a short time period. The reaction conditions are neither acidic nor basic and are mild enough to perform these reactions in the presence of either acid or base sensitive aminals. Furthermore this method is equally effective with aminals bearing electron-withdrawing and electron-donating substituents in the aromatic ring and the yields of products are not affected by the nature of substituent on the phenyl ring (entries 4i, 4j). The reaction also proceeded with a heteroaromatic aminal (entry 4p).

The role of iodine could be the formation of trimethylsilyl iodide [14] in the initial step and subsequently producing weakly solvated anion, which displays high reactivity toward iminium salts generated *in situ*. A plausible mechanism for this transformation is shown in Scheme 2. In conclusion, this method has the advantages of inexpensive reagents, operational simplicity, improved yields, enhanced rates and simple experimental work up procedures.

EXPERIMENTAL

Chemicals and Apparatus

All reactions were performed under argon. Methylene chloride was refluxed and distilled from phosphorus pentoxide. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). Aminals were prepared according to the reported procedures. Most aldeyhdes were distilled before use. Chemicals were purchased from Fluka and Merck and used as received.

IR spectra were taken on Matt Son 1000 Unicam FTIR, ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz Ultra Shield.

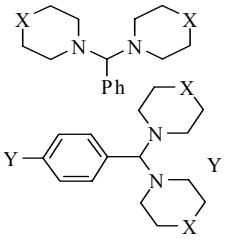
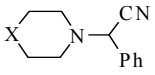
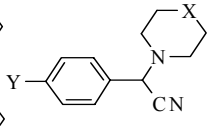
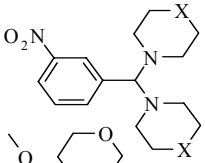
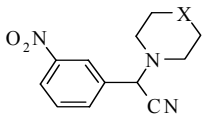
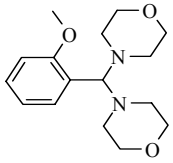
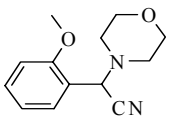
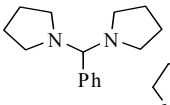
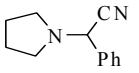
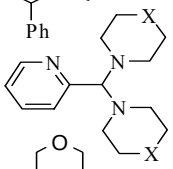
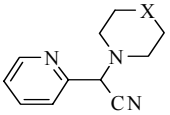
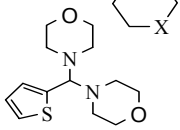
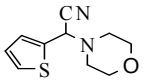
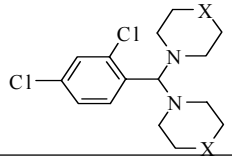
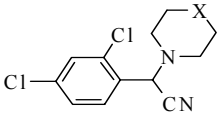
General Procedure for Trimethylsilyl Cyanide Addition to Amina**l.**

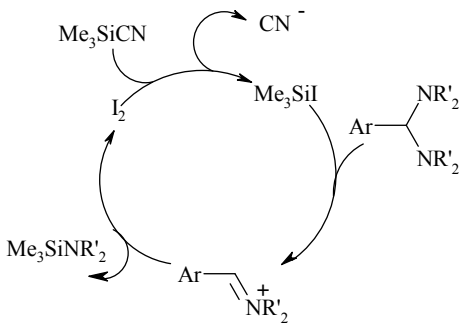
Iodine (0.2 mmol, 0.05 g) was added to a mixture of aminal (1 mmol) and trimethylsilyl cyanide (1.2 mmol) in dry CH_2Cl_2 (2 ml). The mixture was stirred at room temperature for 3 min. The resulting mixture was quenched with aqueous sodium thiosulphate and extracted with CH_2Cl_2 (2 × 10 ml). The combined organic layers washed with a 2 M solution of sodium hydroxide and then with water, dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the almost pure products (Table 1). Further purification was carried out by recrystalization or chromatography on silica gel if needed. All compounds were characterized on the basis of their spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature.

Selected Spectroscopic Data

2-(*N*-Morpholino)-2-phenylacetonitrile (4a) [11b]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.57-2.58 (m, 4 H), 3.70-3.75

Table 1. Cyanoamination of Aldehydes in the Presence of Iodine

Substrate	Product		Yield (%)
		**4a**, X = O	97
		4b, X = CH_2	96
		Y = Cl **4c**, X = O	96
		Y = Cl **4d**, X = CH_2	96
		Y = Br **4e**, X = O	98
		Y = Br **4f**, X = CH_2	98
		Y = NO_2 **4g**, X = O	99
		Y = NO_2 **4h**, X = CH_2	97
		Y = OMe **4i**, X = CH_2	96
		**4j**, X = O	98
		4k, X = CH_2	96
		**4l**	99
		**4m**	96
		**4n**, X = O	98
		4o, X = CH_2	99
		**4p**	98
		**4r**, X = O	96
		4s, X = CH_2	96



Scheme 2

(m, 4H),4.80 (s, 1H), 7.37-7.54 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$), δ, 50.3 (CH), 62.7 (CH_2), 67.1 (CH_2) 115.6 (CN), 127.5 (CH), 128.4 (CH), 130.3 (CH), 132.1 (C); IR, (CH_2Cl_2), 2230 (CN) cm^{-1}.

2-(*N*-Piperidino)-2-phenylacetonitrile (4b) [11b]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 1.45-1.60 (m, 6 H), 2.49 (m, 4H), 4.81 (s, 1H), 7.33-7.38 (m, 3H), 7.52-7.54 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$), δ, 24.3 (CH_2), 26.2 (CH_2), 51.3 (CH), 63.2 (CH_2), 115.9 (CN), 128.2 (CH), 128.8 (CH), 129.3 (CH), 135.1 (C); IR, (CH_2Cl_2), 2232 (CN) cm^{-1}.

2-(*N*-Morpholino)-2-(*p*-chlorophenyl)acetonitrile (4c) [13d]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.58-2.63 (m, 4H), 3.66-3.69 (m, 4H), 5.01 (s, 1H), 7.12-7.21 (m, 2H), 7.24-7.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ, 50.3 (CH), 63.9 (CH_2), 66.2 (CH_2), 115.7 (CN), 128.6 (CH), 129.3 (CH) 133.4 (CH), 138.4 (C); IR (CH_2Cl_2), 2233 cm^{-1}.

2-(*N*-Morpholino)-2-(*p*-bromophenyl)acetonitrile (4e) [13d]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.53-2.54 (m, 4H), 3.67-3.71 (m, 4H), 4.76 (s, 1H), 7.38 (m, 2H), 7.51(m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ, 50.3 (CH), 62.1 (CH_2), 66.8 (CH_2), 114.6 (CN), 123.6 (C), 129.3 (CH),132.0 (C), 133.6 (CH), IR (CH_2Cl_2), 2235 cm^{-1}.

(*N*-Morpholino)-2-(*m*-nitrophenyl)acetonitrile (4j) [6h]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.55-2.62 (m, 4H), 3.71-3.75 (m, 4H), 4.95 (s, 1H), 7.62 (m, 1H), 7.92 (m,1H), 8.22 (m, 1H), 8.38 (m,1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ 50.1 (CH), 64.9 (CH_2), 67.2 (CH_2), 114.9 (CN), 123.2 (CH), 123.7 (C) 134.6 (CH), 135.4 (CH), 139.8 (CH), 148.4 (C); IR (CH_2Cl_2), 1347, 1534, 2235cm^{-1}.

2-(*N*-Morpholino)-2-(2-methoxyphenyl) acetonitrile (4l) [11b]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.59-2.63 (m, 4H), 3.66-3.70 (m, 4H), 3.84 (s, 3H), 5.10(s, 1H), 6.93-7.00 (m, 2H), 7.34-7.46 (m, 2H); δ ^{13}C NMR (125 MHz, $CDCl_3$) δ, 50.1 (CH), 64.9 (CH_2), 67.2 (CH_2), 114.9 (CN), 111.4 (CH), 120.8 (CH), 122.8 (C), 129.4 (CH), 131.4 (CH) 157.4 (C); IR (CH_2Cl_2), 2235 cm^{-1}.

2-(*N*-Pyrrolidino)-2-phenylacetonitrile (4m) [11b]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 1.80-1.81 (m, 4H), 2.66-2.72 (m, 4H), 5.30 (s, 1H), 7.25-7.35 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$), δ, 50.1 (CH), 64.9 (CH_2), 67.2 (CH_2), 114.9 (CN), 124.0 (CH), 125.8 (CH), 130.8 (CH), 135.4 (CH), 140.4 (C); IR (CH_2Cl_2), 2239cm^{-1}.

2-(*N*-Morpholino)-2-(pyridin-2-yl)acetonitrile (4n) [12d]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.59-2.66 (m, 4H), 3.70-3.76 (m, 4H), 4.93 (s, 1H), 7.28-8.63 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ, 50. 5 (CH), 64.9 (CH_2), 115.1 (CN), 123.0 (CH), 124.3 (CH), 137.6 (CH), 150.1 (CH), 152.7 (C); IR (CH_2Cl_2), 2229 (CN) cm^{-1}.

2-(*N*-Morpholino)-2-(2-thienyl)acetonitrilen (4p) [13d]. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 2.56-2.67 (m, 4H), 3.71-3.77 (m, 4H), 4.96 (s, 1H), 6.98 (m, 1H), 7.24 (m, 1H), 7.35 (m, 1H); IR (CH_2Cl_2), 2232 cm^{-1}.

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