Synthetic Communications®, 37: 2543–2548, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701462732

Ferric Perchlorate–Catalyzed One-Pot Synthesis of α-Aminonitriles using Trimethylsilylcyanide

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

Abstract: A simple and efficient one-pot method has been developed for the synthesis of α-aminonitriles from aldehydes, amines, and trimethylsilyl cyanide in the presence of a catalytic amount of ferric perchlorate.

Keywords: aldehydes, amines, α-aminonitriles, ferric perchlorate, trimethylsilyl cyanide

α-Aminonitriles are important intermediates for the synthesis of α-amino acids[1] and various nitrogen-containing heterocycles[2] such as imidazoles and thiadiazoles. They are usually prepared by the nucleophilic addition of cyanide anion to the imines.[3] The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution. Subsequently, several modifications of the Strecker reaction have been reported using a variety of cyanating agents such as α-trimethylsiloxynitriles and diethyl phosphorocyanidate under various reaction conditions.[4] The use of trimethylsilyl cyanide is a safer and more effective cyanide anion source for the nucleophilic addition reactions of imines under mild conditions.[5] However, many of these methods involve the use of expensive reagents and extended reaction times, harsh conditions, and tedious aqueous workup, leading to the generation of

Received in Poland October 6, 2006
Address correspondence to Majid M. Heravi, Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran. E-mail: mmh1331@yahoo.com

a large amount of toxic waste. Also, recent one-pot procedures have been developed for this transformation.[6]

Recently we have reported the ability of ferric perchlorate as catalyst for transformations in organic syntheses.[7] In continuation of our work to develop new synthetic methodologies,[8] we herein report that ferric perchlorate, which acts as a mild Lewis acid, might be a useful and inexpensive catalyst for the synthesis of α-aminonitrile.

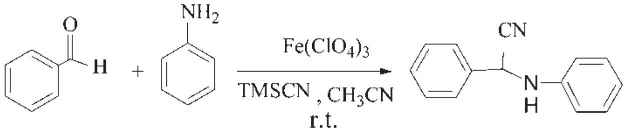
The reaction of aldehydes and amines with trimethylsilylcyanide (TMSCN) in the presence of a catalytic amount of ferric perchlorate afforded the corresponding α-aminonitriles in acetonitrile as a solvent in high yields (Scheme 1, Table 1). The reaction is successful using amines with a variety of aldehydes but not ketones. These three-component coupling reactions proceeded efficiently at ambient temperature with high selectivity. No cyanohydrin trimethylsilyl ethers (an adduct between an aldehyde and trimethylsilyl cynide) were obtained under these reaction conditions. This is because of the rapid formation and activation of the imines by ferric perchlorate. 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 summary, we describe a simple, convenient, and practical method for the synthesis of α-aminonitriles through a one-pot, three-component coupling of aldehydes, amines, and trimethylsilyl cyanide using ferric perchlorate. The major advantage of this method is that it is truly a one-pot procedure that 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 nontoxic reagents and solvents.

EXPERIMENTAL

General Procedure for the Preparation of α-Aminonitriles

A mixture of aldehyde (1 mmol), amine (1 mmol), trimethylsilyl cyanide (1.1 mmol), and $Fe(ClO_4)_3$ (0.1 mmol, 0.05 g) in acetonitrile (5 mL) was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction, as monitored by thin-layer chromatography (TLC), a



Scheme 1.

Table 1. Ferric perchlorate–promoted synthesis of α-aminonitriles using trimethylsilyl cyanide

Entry	Aldehyde	Amine	Time (h)	Mp (°C) Observed	Mp (°C) Found	Yield (%)
1	Benzaldehyde	Aniline	3.0	70–73	73–74[9]	95
2	Benzaldehyde	Furfurylamine	3.0	Oil	Yellow liq.[9]	83
3	4-Chlorobenzaldehyde	Aniline	4.0	105–108	109–112[9]	94
4	4-Chlorobenzaldehyde	4-Chloroaniline	2.5	90–102	—	95
5	4-Chlorobenzaldehyde	Furfurylamine	2.0	Oil	—	70
6	2- Chlorobenzaldehyde	4-Chloroaniline	5.0	95–100	—	90
7	2- Chlorobenzaldehyde	Aniline		150–158	—	80
8	4-Methyl benzaldehyde	Aniline	4.0	74–76	76–78[9]	92
9	4-Methyl benzaldehyde	4-Chloroaniline	4.0	103–110	—	88
10	4-Methoxybenzaldehyde	Aniline	3.0	92–96	94–95[9]	96
11	2-Ethoxybenzaldehyde	Furfurylamine	3.0	Oil	Yellow liq.[9]	83
12	4-Isoprpylbenzaldehyde	Aniline	3.0	63–72	—	94
13	4-Isoprpylbenzaldehyde	Furfurylamine	2.5	Oil	—	97
14	4-Nitrobenzaldehyde	Furfurylamine	5.0	Oil	—	85
15	4-Nitrobenzaldehyde	4-Chloroaniline	6.0	160–200	—	80
16	2-Naphtaldehyde	4-chloroanilin	5.0	115–120	—	91
17	4-Methoxybenzaldehyde	4-chloroanilin	4.0	71–77	—	86

10% $NaHCO_3$ solution (15 mL) was added. Workup and purification over silica gel gave the corresponding α-aminonitriles in high yields.

Spectral Data for Selected Compounds

2-(N-Anilino)-2-(4-chlorophenyl)acetonitrile (entry 3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (br s, 1H), 5.39 s, 1H), 6.75 (d, $J = 8$ Hz, 2H), 6.91 (t, $J = 7.8$ Hz, 1H), 7.15 (t, $J = 7.9$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz, 2H), 7.61 (d, $J = 8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 114.2, 117.7, 120.8, 128.5, 129.4, 129.6, 132.3, 135.5, 144.4; EIMS m/z 242 and 244 (M +), 149, 114, 91, 77, 59.

2-(N-furfurylamino)-2-phenylacetonitrile (entry 2). ^{1}H NMR (300 MHz, $CDCl_3$) 1.82 (br s, 1H), 4.01 (s, 2H), 4.79 (s, 1H), 6.21–6.41 (m, 2H), 7.31–7.56 (m, 6H); EIMS m/z 212 (M +), 186, 81, 77.

REFERENCES

1. Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. Synthesis and properties of α-Aminonitriles. *Russ. Chem. Rev.* **1989**, *58*, 148.
2. (a) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. A general synthetic system for 1,2,5-thiadiazoles. *J. Org. Chem.* **1967**, *32*, 2823; (b) Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. Antihypertensive agent: Synthesis and biological properties of 2-amino-4-aryl-2-imidazolines. *J. Med. Chem.* **1973**, *16*, 901.
3. (a) Strecker, A. General catalyst for the asymmetric Strecker reaction. *Ann. Chem. Pharm.* **1850**, *75*, 27; (b) Mai, K.; Patil, G. Facile synthesis of aminonitriles. *Tetrahedron Lett.* **1984**, *25*, 4583; (c) Harusawa, S.; Hamada, Y.; Shioiri, T. Diethyl phosphorocyanidated (DEPC): A novel reagent for the classical Strecker's α-amino nitrile synthesis. *Tetrahedron Lett.* **1979**, *20*, 4663.
4. (a) Mai, K.; Patil, G. Facile synthesis of aminonitriles. *Tetrahedron Lett.* **1984**, *25*, 4583; (b) Harusawa, S.; Hamada, Y.; Shioiri, T. Diethyl phosphorocyanidated (DEPC): A novel reagent for the classical Strecker's a-amino nitrile synthesis. *Tetrahedron Lett.* **1979**, *20*, 4663.
5. (a) Chakraborty, T. K.; Reddy, G. V.; Hussain, K. A. Diastereoselective Strecker synthesis using α-phenylglycinol as chiral auxiliary. *Tetrahedron Lett.* **1991**, *32*, 7597; (b) Leblanc, J.; Gibson, H. W. Synthesis of α-aminonitriles by self-catalyzed, stoichiometric reaction of primary amines, aldehydes, and trimethylsily cyanide. *Tetrahedron Lett.* **1992**, *33*, 6295; (c) Heydari, A.; Fatemi, P.; Alizadeh, A. Lithium perchlorate/diethylether–catalyzed aminocyanation of aldehydes. *Tetrahedron Lett.* **1998**, *39*, 3049.
6. (a) Kobayashi, S.; Ishitani, H.; Ueno, M. Facile synthesis of α-amino nitriles using lanthanide triflate as a Lewis acid catalyst. *Synlett* **1997**, 115; (b) Kobayashi, S.; Busujima, T.; Nagayama, S. Scandium triflate–catalyzed Strecker-type reactions of aldehydes, amines, and tributyltin cyanide in both organic and aqueous solutions: Achievement of complete recovery of the tin compounds toward

environmentally friendly chemical. *J. Chem. Soc., Chem. Commun.* **1998**, 981; (c) Subba Reddy, B. V.; Eeshwaraiah, B.; Srinivas, M. Montmorillonite KSF clay catalyzed one-pot synthesis of α-aminonitriles. *Tetrahedron* **2004**, *60*, 1767–1771; (d) De, S. K.; Gibbs, R. A. Bismuth trichloride catalyzed synthesis of α-aminonitriles. *Tetrahedron Lett.* **2004**, *45*, 7407–7408; (e) De, S. K. Nickel(II) chloride catalyzed one-pot synthesis of α-aminonitriles. *J. Mol. Cata. A: Chem.* **2005**, *225*, 169–171; (f) Ranu, B. C.; Dey, S. S.; Hajra, A. Indium trichloride catalyzed one-step synthesis of α-amino nitriles by a three-component condensation of carbonyl compounds, amines and potassium cyanide. *Tetrahedron* **2002**, *58*, 2529–2532; (g) Martínez, R.; Ramó, D. J.; Yus, M. Catalyst-free multicomponent Strecker reaction in acetonitrile. *Tetrahedron Lett.* **2005**, *46*, 8471–8474.

7. (a) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Hekmatshoar, R. Mild and efficient tetrahydropyranylation of alcohols and dehydropyranylation of THP ethers catalyzed by ferric perchlorate. *Tetrahedron Lett.* **2005**, *46*, 2543–2545; (b) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Hekmatshoar, R. Catalytic aromatization of Hantzsch 1,4-dihydropyridines by ferric perchlorate in acetic acid. *Tetrahedron Lett.* **2005**, *46*, 2775–2777; (c) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Hekmatshoar, R. Ferric perchlorate: A novel and highly efficient catalyst for direct acetylation of THP ethers with acetic acid. *J. Mol. Cat. A: Chem.* **2006**, *244*, 8–10; (d) Heravi, M. M.; Behbahani, F. K.; HekmatShoar, R.; Oskooie, H. A. Catalytic acetylation of alcohols and phenols with ferric perchlorate in acetic acid. *Catal. Commun.* **2006**, *7*, 136–139; (e) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Hekmatshoar, R. Ferric perchlorate catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-Ones and thiones: An expedient protocol for the Biginelli reaction. *Mendeleev Commun.* Submitted.
8. (a) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Gharib, A.; Jahangir, M. Preyssler catalyst $[NaP_5W_{30}O_{110}]^{14-}$: A green, efficient and reusable catalyst for esterification of salicylic acid with aliphatic and benzylic alcohols. *Appl. Cata.* **2006**, *302*, 42; (b) Heravi, M. M.; Hekmatshoar, R.; Pedram, L. Synthesis of N-arylphthalimides catalyzed by 1,4-diazabicyclo[2,2,2]octane [DABCO] in solventless system. *J. Mol. Catal. A: Chem.* **2005**, *231*, 89; (c) Asadolah, K.; Heravi, M. M. Bismuth (III) nitrate supported onto silica gel, a new catalyst for acetylation of alcohols and phenols under microwave irradiation. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 2335–2339; (d) Bigdeli, M. M.; Nahid, M. A.; Ajami, D. Sulphuric acid adsorbed on silica gel: An efficient catalyst for the protection and deprotection of alcohols with dihydropyran. *Indian. J. Chem. Sect.* **1999**, *38*, 1285–1286; (e) Heravi, M. M.; Bakhtiari, K.; Bamoharram, F. F. 12-Molybdophosphoric acid: A recyclable catalyst for the synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1H)-ones. *Catal. Commun.* **2006**, *7*, 373; (f) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Gharib, A.; Jahangir, M. A catalytic method for synthesis of γ-butyrolactone, ε-caprolactone and 2-cumaranone in the presence of Preyssler's anion, $[NaP_5W_{30}O_{110}]^{14-}$, as a green and reusable catalyst. *J. Mol. Catal. A: Chem.* **2006**, *252*, 90; (g) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Tavakoli, N. N-oxidation of pyridine carboxylic acids using hydrogen peroxide catalyzed by a green heteropolyacid catalyst: Preyssler's anion, $[NaP_5W_{30}O_{110}]^{14}$. *J. Mol. Catal. A: Chem.* **2006**, *252*, 219; (h) Tajbakhsh, M.; Heravi, M. M.; Mohajerani, B.; Ahmadi, A. N. Natural HEU type zeolite catalyzed Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1H) one derivatives. *J. Mol. Catal. A:*

Chem. **2005**, *236*, 213; (i) Heravi, M. M.; Motamedi, R.; Siefi, N.; Bamoharram, F. F. Catalytic synthesis of 6-aryl-1H-pyrazolo[3,4-d]pyrimidin-4[5H]-ones by heteropolyacid: $H_{14}[NaP_5W_{30}O_{110}]$ and $H_3PW_{12}O_{40}$. *J. Mol. Catal.* **2006**, *249*, 1; (j) Oskooie, H. A.; Heravi, M. M.; Bakhtiari, K.; Zadsirjan, V.; Bamoharram, F. F. $H_{14}[NaP_5W_{30}O_{110}]$ as an efficient catalyst for the one-pot synthesis of α-amino nitriles. *Synlett* **2006**, 1768–1770.

9. Yadav, J. S.; Subba Reddy, B. V.; Eeshwaraiah, B.; Srinivas, M. Montmorillonite KSF clay catalyzed one-pot synthesis of α-aminonitriles. *Tetrahedron* **2004**, *60*, 1767–1771.