

# Lithium perchlorate suspend in methylene chloride, a mild, efficient and reusable catalyst for the synthesis of ferrocene aminonitrile derivatives

Rozbeh Yousefi, Najmedin Azizi, Mohammad R. Saidi \*

Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran 11365, Iran

Received 12 July 2004; accepted 18 August 2004

Available online 25 September 2004

## Abstract

A practical and efficient method for the synthesis of  $\alpha$ -aminonitriles of ferrocene by one-pot three-component reaction of ferrocenecarboxaldehyde, trimethylsilyl cyanide and amines catalyzed by lithium perchlorate suspend in  $\text{CH}_2\text{Cl}_2$  is reported under mild and neutral reaction conditions in high yields and short reactions times.

© 2004 Elsevier B.V. All rights reserved.

**Keywords:** Trimethylsilyl cyanide; Ferrocenecarboxaldehyde; Lithium perchlorate,  $\alpha$ -Aminonitriles of ferrocene

## 1. Introduction

The Mannich reaction provides an excellent method for carbon–carbon bond formation and its importance were reflected in the ever-increasing number of suitable substrate and reaction conditions, which have been developed since long ago [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], trifluoroacetic anhydride with *N*-oxides [4] and trichloromethylsilane with aminal and aminol ethers [5].

The Strecker reaction provides one of the most efficient methods for the synthesis of  $\alpha$ -aminonitriles, which are useful intermediates in the synthesis of amino acids [6] and nitrogen containing heterocycles, such as thia-

zoles, imidazoles, etc. with biological activities [7]. Moreover,  $\alpha$ -aminonitriles derived from ferrocenecarboxaldehyde are used as chiral auxiliaries in some asymmetric syntheses such as the Ugi four-component condensation reaction, and the potential of these compounds as new types of ligands has been reported recently in copper-catalyzed reaction [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  $\alpha$ -trimethylsilyloxynitriles and diethyl phosphorocyanidate under various reaction conditions [11]. Trimethylsilylcyanide (TMSCN) is a cyanide anion source, which provides promising and safer routes to these compounds [12]. There are two common reported methods for the synthesis of aminonitriles of ferrocene in the literature; nucleophilic displacement of acetate with methanolic amines in the corresponding acetoxy ferrocenylacetonitriles and one-pot reaction of ferrocene-carboxaldehyde,  $\text{NaHSO}_3$ ,  $\text{NaCN}$  and amines. However, the reported procedures have long

\* Corresponding author. Tel.: +98 21 600 5718; fax: +98 21 601 2983.

E-mail address: [saidi@sharif.edu](mailto:saidi@sharif.edu) (M.R. Saidi).

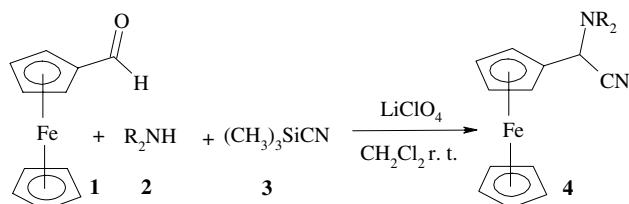
reaction time, tedious work up conditions and low yields in the latter case [9].

Therefore, the development of novel and practical method for the cyanation under mild conditions has attracted much attention in organic synthesis.

Recently, concentrated solutions of  $\text{LiClO}_4$  in diethyl ether (LPDE) have been used in various organic transformation [13,14]. On the other hand, a catalytic amount of  $\text{LiClO}_4$  suspended in dichloromethane has also been reported to provide a mild and effective medium for some well-known reactions, such as Mannich, Mukaiyama aldol, or Diels–Alder reactions [15]. In this paper, a much more simple, general and new catalytic route for the synthesis of  $\alpha$ -aminonitriles of ferrocene via one-pot three component reactions of amine, ferrocenecarboxaldehyde and trimethylsilyl cyanide in dichloromethane in the presence of catalytic amount of  $\text{LiClO}_4$  is described.

In the first step, we used catalytic amount of  $\text{LiClO}_4$  in a range of different solvents at room temperature. Among the solvents examined (acetonitrile, dichloromethane, acetone, toluene and petroleum ether),  $\text{CH}_2\text{Cl}_2$  gave the best result. Concentrated solution of LPDE (ca. 5 M) also gave the corresponding  $\alpha$ -aminonitriles of ferrocene in good yields, but preparation and handling of 5 M  $\text{LiClO}_4$  solution in ether is an inherent disadvantage of such a reaction. Optimum conditions found to be 2 equivalent of  $\text{LiClO}_4$  in  $\text{CH}_2\text{Cl}_2$  as solvent. With these results in hand, addition of  $\text{TMSCN}$  in the presence of catalytic amount of  $\text{LiClO}_4$  to other iminium salts or imines, prepared in situ, were studied using the optimal reaction conditions, Scheme 1. In all cases, a nearly quantitative conversion of the iminium salts or imines to the corresponding  $\alpha$ -aminonitriles of ferrocene was observed. The reactions are clean and highly selective for affording exclusively  $\alpha$ -aminonitriles of ferrocene in high yields and short time. The reaction conditions are mild enough to perform these reactions in the presence of either acid or base sensitive functional groups. Furthermore, this method is equally effective for the aromatic, aliphatic, hindered, and unhindered amines. The yields of products were not affected by the nature of amines. A summary of the results is shown in Table 1.

In conclusion, this method has the advantages of inexpensive reagents, simple operation, improved yields, enhanced rates and simple experimental work up procedures.



Scheme 1.

Table 1  
 $\alpha$ -Aminonitriles derived from ferrocenecarboxaldehyde

$-\text{NR}_2$						
Yields	100	98	100	100	100	98
$-\text{NR}_2$						
Yields	95	93 <sup>a</sup>	96	95	(S)- 98 <sup>b</sup>	(R)- 98 <sup>b</sup>

<sup>a</sup> Reaction time 80 min.

<sup>b</sup> de 100:0 (measured by NMR).

## 2. Experimental

### 2.1. General

IR spectra were taken on Matt Son 1000 Unicam FTIR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker 500 MHz Ultra Shield. All reactions were performed under argon. Dichloromethane was refluxed and distilled over phosphorus pentoxide. Column chromatography was performed on Merck silica gel 60. Chemicals were purchased from Fluka, Merck, and used as received.

### 2.2. General procedure

The ferrocenecarboxaldehyde (0.5 mmol),  $\text{LiClO}_4$  (1 mmol) and  $\text{CH}_2\text{Cl}_2$  (3 mL) were placed in a 50 mL flask and stirred for 3 min, then an amine (0.8 mmol) were added via syringe, after 5 min,  $\text{TMSCN}$  (0.7 mmol) was added and the mixture was stirred at r.t. for about 20–30 min, after the completion of the reaction,  $\text{CH}_2\text{Cl}_2$  (10 mL) was added, and lithium perchlorate was filtered off. Then the organic layer washed with aqueous  $\text{NaHCO}_3$  ( $2 \times 10$  mL), water ( $2 \times 10$  mL), and dried over  $\text{Na}_2\text{SO}_4$ . The reaction product was recovered by simple removal of solvent and purified by column chromatography on silica gel, eluting with petroleum ether/ $\text{EtOAc}$ , if necessary. All compounds were characterized on the basis of their spectroscopic data (IR, NMR), and by comparison with those reported in the literature [9,10].

#### 2.2.1. Caution

Although we did not have any accident while using  $\text{LiClO}_4$ , it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

#### 2.2.2. Spectroscopic data

**4k:**  $\delta$  1.47 (d,  $J = 6.4$  Hz, 3H), 1.87 (br, NH), 4.09–4.50 (m, 11H), 7.30–7.46 (m, 5H); **4l:**  $\delta$  1.47 (d,  $J = 6.5$  Hz, 3H), 1.61 (br, NH), 4.09–4.46 (m, 11H), 7.30–7.45 (m, 5H).

## Acknowledgement

We are grateful to Volkswagen-Stiftung (I/78849) Federal Republic of Germany, for financial support towards the purchase of equipments and chemicals.

## References

- [1] (a) F.F. Blike, *Org. Reaction* 1 (1942) 303;  
H. Hellman, G. Opitz, *Angew. Chem.* 68 (1956) 265;  
(b) M. Arend, B. Westermann, N. Risch, *Angew. Chem., Int. Ed.* 37 (1998) 1044;  
(c) S. Kobayashi, H. Ishitani, *Chem. Rev.* 99 (1999) 1069.
- [2] (a) H. Bohme, D. Eichler, *Arch. Pharm.* 300 (1967);  
(b) A.P. Kozikowski, H. Ishida, *Heterocycles* 14 (1980) 55.
- [3] G. Kinast, L.F. Tietze, *Angew. Chem., Int. Engl.* 15 (1976) 239.
- [4] A. Ahond, A. Cave, C. Kan-Fun, P. Potier, *Bull. Soc. Chim. Fr.* 2707 (1970).
- [5] H. Heaney, G. Papageorgiou, R.-F. Wilkins, *Tetrahedron* 53 (1997) 13361.
- [6] (a) A. Strecker, *Ann. Chem. Pharm.* 75 (1850) 27;  
(b) Y.M. Shafran, V.A. Bakulev, V.S. Mokrushin, *Russ. Chem. Rev.* 58 (1989) 148;  
(c) P.L. Serrano, J.A. Jongejan, F. Rantwijk, R.A. Sheldon, *Tetrahedron* 12 (2001) 219;  
(d) N. Nakajima, M. Ubukuta, *Tetrahedron Lett.* 38 (1997) 2099;  
(e) G.A. Olah, S.C. Narang, A.P. Fung, B.G.B. Gupta, *Synthesis* (1980) 657;  
(f) G. Dyker, *Angew. Chem., Int. Ed. Engl.* 36 (1997) 1700;  
(g) S. Yokoshima, H. Tokuyama, T. Fukuyama, *Angew. Chem., Int. Ed.* 39 (2000) 4073;  
(h) S. Yokoshima, T. Kubo, H. Tokuyama, T. Fukuyama, *Chem. Lett.* 122 (2002).
- [7] L.M. Weinstock, P. Davis, B. Handelsman, R. Tull, *J. Org. Chem.* 32 (1967) 2823.
- [8] (a) T. Hayashi, M. Kumada, *Acc. Chem. Res.* 15 (1982) 395;  
(b) T. Hayashi, *Pure Appl. Chem.* 60 (1988) 7;  
(c) M. Sawamura, Y. Ito, *Chem. Rev.* 92 (1992) 857.
- [9] A. Patti, G. Nicolosi, J.A.S. Howell, K. Humphries, *Tetrahedron* 9 (1998) 4381, and reference cited there in.
- [10] Y.M. Shatran, V.A. Bakulev, V.S. Mokrushin, *Russ. Chem. Rev.* 58 (1989) 148.
- [11] (a) K. Mai, G. Patil, *Tetrahedron Lett.* 25 (1984) 4583;  
(b) S. Harusawa, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* 20 (1979) 4663;  
(c) K. Mai, G. Patil, *Synth. Commun.* 15 (1985) 157;  
(d) M. Mori, H. Imma, T. Nakai, *Tetrahedron Lett.* 38 (1997) 6229;  
(e) J. Mulzer, A. Meier, J. Buschmam, P. Luger, *Synthesis* 123 (1996).
- [12] (a) T.K. Chakraborty, G.V. Reddy, K.A. Hussain, *Tetrahedron Lett.* 32 (1991) 7597;  
(b) J.P. Leblanc, H.W. Gibson, *Tetrahedron Lett.* 33 (1992) 6295;  
(c) E. Leclerc, M. Mangeney, V. Henryon, *Tetrahedron* 11 (2000) 3471;  
(d) P. Sun, C. Qian, L. Wang, R. Chen, *Synth. Commun.* 32 (2002) 2973.
- [13] (a) M.R. Saidi, N. Azzizi, *Synlett* 1347 (2002);  
(b) N. Azizi, M.R. Saidi, *Tetrahedron* 60 (2004) 383.
- [14] S. Sankararaman, J.E. Nesakumar, *Eur. J. Org. Chem.* 2003 (2000).
- [15] (a) M.R. Saidi, M. Nazari, *Monatsh. Chem.* 135 (2004) 309;  
(b) M.T. Reetz, D.N.A. Fox, *Tetrahedron Lett.* 34 (1994) 1119;  
(c) M.D. Dowle, R. Hayes, D.B. Judd, C.N. Williams, *Synthesis* 73 (1983);  
(d) M.C. Cooper, H. Heaney, *Tetrahedron Lett.* 27 (1986) 5011;  
(e) H. Heaney, G. Papageorgiou, R.F. Wilkins, *Tetrahedron Lett.* 29 (1988) 2377.