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Tetrahedron Letters 49 (2008) 640–644

Tetrahedron Letters

$Fe(Cp)_2PF_6$ catalyzed efficient Strecker reactions of ketones and aldehydes under solvent-free conditions

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Received 8 October 2007; revised 15 November 2007; accepted 22 November 2007

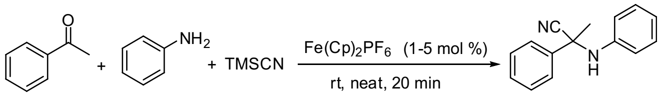
Abstract

The synthesis of α-aminonitriles of ketones and aldehydes was performed in very short reaction times (20 min) with excellent yields in the presence of 5 mol % of $Fe(Cp)_2PF_6$ under solvent-free conditions.

Keywords: Strecker reaction; Aldehydes; Ketones; $Fe(Cp)_2PF_6$; Solvent-free

α-Aminonitriles are valuable intermediates for the synthesis of α-amino acids[1] and a variety of nitrogen-containing heterocycles[2] such as imidazoles and thiadiazoles. These are versatile synthons in organic chemistry[3]. In general, α-aminonitriles are prepared[4] by the reaction of aldehydes/ketones with amines in the presence of a cyanide source such as HCN,[3] KCN,[5a] TMSCN,[5b], $(EtO)_2P(O)CN$,[5c] Et_2AlCN[5d] and Bu_3SnCN,[5e] which are often hazardous, toxic and involve harsh reaction conditions.[6] Lewis acids such as $Cu(OTf)_2$,[7] $BiCl_3$,[8] $NiCl_2$,[9] $InCl_3$,[10] $RuCl_3$,[11] $Sc(OTf)_3$,[12] $La(NO_3)_3{\cdot}6H_2O$ or $GdCl_3{\cdot}6H_2O$[13] and I_2[14] in stoichiometric or catalytic amounts have been used to catalyze the Strecker reaction under milder conditions with aldehydes, and there are also a few reports not using these as a catalyst.[15] Solid catalysts such as, heteropoly acids,[16] Montmorillonite KSF clay,[17] and guanidine hydrochloride [18] have been employed with aldehydes only for the synthesis of α-aminonitriles. For ketones, Matsumoto[19] reported the synthesis of α-aminonitriles at very high pressure in long reaction times, while Olah and coworkers[20] used Ga(III) triflate in dichloromethane. Water as reaction medium was also reported for preparing α-aminonitriles,[5f] but due to the reversible nature of the reaction, unreacted starting materials remained along with cyanohydrins as by-products. This made the isolation of pure α-aminonitriles difficult under aqueous conditions. Therefore, a system devoid of solvent[21] or using a non-hazardous solvent, for the synthesis of α-aminonitriles in good yields using ketones as substrates and short reaction times would

Table 1
The effect of catalyst loading on the one-pot synthesis of α-aminonitriles under solvent-free conditions[a]



Entry	Mol [%]	Yield[b] [%]
1	1	78
2	2.5	86
3	5	94[c]

[a] $Fe(Cp)_2PF_6$ (1–5 mol %), acetophenone (1 mmol), aniline (1 mmol) and TMSCN (1.3 mmol); reaction time 20 min.
[b] Isolated yields.
[c] Complete conversion on TLC.

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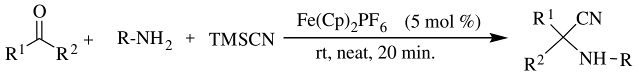
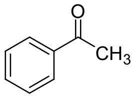
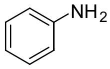
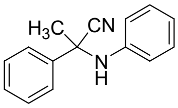
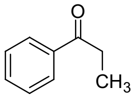
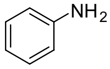
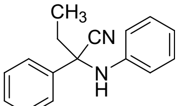
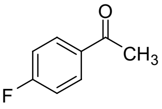
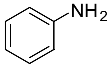
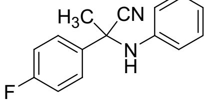
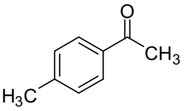
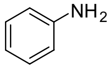
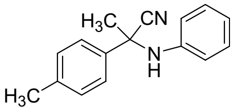
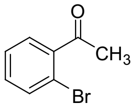
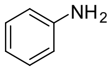
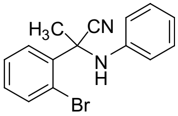
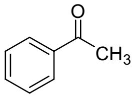
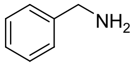
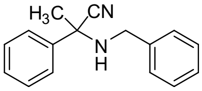
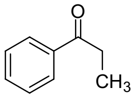
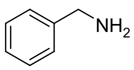
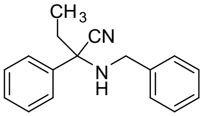
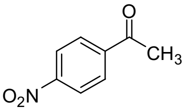
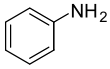
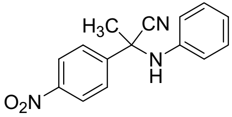
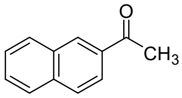
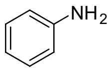
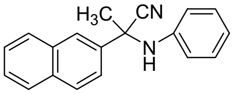
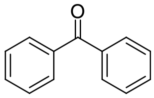
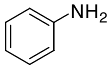
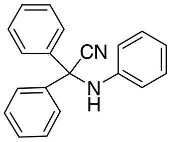
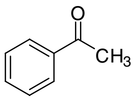
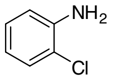
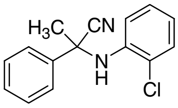
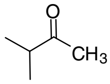
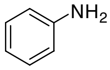
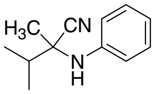
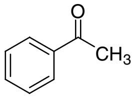
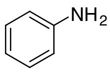
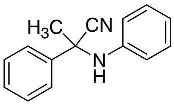
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.11.136

Table 2
One-pot synthesis of α-aminonitriles from various ketones catalyzed by $Fe(Cp)_2PF_6$ under solvent-free conditions[a]



Entry	Ketone	Amine	Product	Yield[b][%]
1				94
2				92
3				82
4				86
5				81
6				90
7				89
8				79
9				88
10				68
11				73
12				78
13				90[c]

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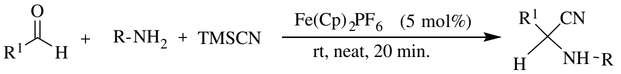
[a] $Fe(Cp)_2PF_6$ (5 mol %), ketone (1 mmol), aniline (1 mmol) and TMSCN (1.3 mmol); reaction time 20 min.

[b] Isolated yield.

[c] Using 10 mmol ketone.

Table 3
One-pot synthesis of α-aminonitriles from various aldehydes catalyzed by $Fe(Cp)_2PF_6$ under solvent-free conditions[a]



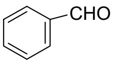
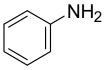
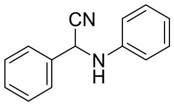
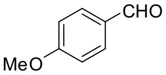
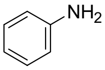
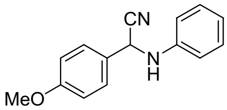
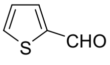
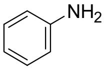
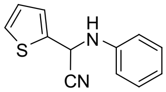
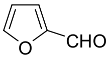
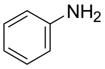
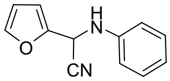
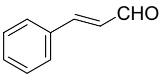
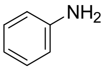
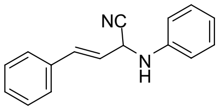
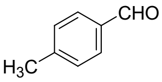
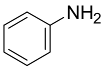
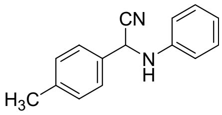
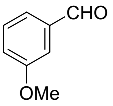
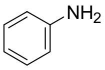
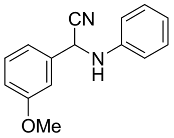
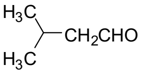
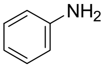
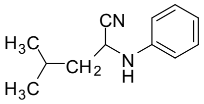
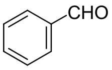
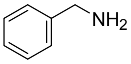
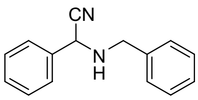
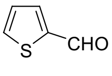
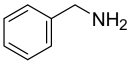
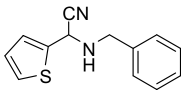
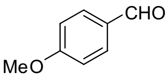
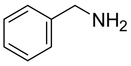
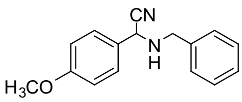
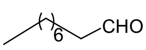
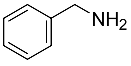
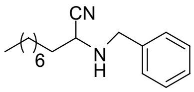
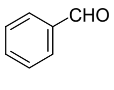
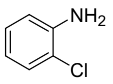
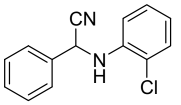
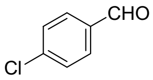
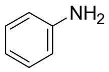
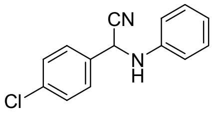
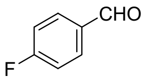
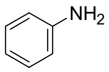
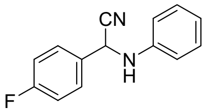
Entry	Aldehyde	Amine	Product	Yield[b] [%]
1				94
2				85
3				86
4				82
5				68
6				84
7				87
8				84
9				80
10				93
11				81
12				65

Table 3 (*continued*)

Entry	Aldehyde	Amine	Product	Yield[b] [%]
13				90
14				91
15				89

[a] $Fe(Cp)_2PF_6$ (5 mol %), aldehyde (1 mmol), aniline (1 mmol) and TMSCN (1.3 mmol); reaction time 20 min.
[b] isolated yields.

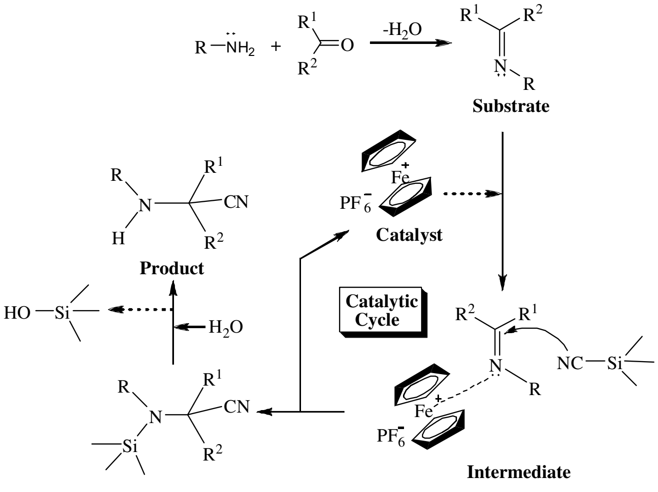
be of interest.[22] Previously, we reported the use of $Fe(Cp)_2PF_6$ as a catalyst for the cyanosilylation of carbonyl compounds under solvent-free conditions[23] and here we report the utility of $Fe(Cp)_2PF_6$ as a catalyst to produce α-aminonitriles of ketones in high yields under solvent-free conditions at room temperature with various amines. To establish the generality of the reaction, we have also extended this protocol to aldehydes.

$Fe(Cp)_2PF_6$ (1–5 mol %) with acetophenone, TMSCN and aniline as a representative substrate, gave the corresponding α-aminonitrile in 94% yield with a catalyst loading of 5 mol % within 20 min (Table 1, entry 3) under solvent-free conditions at room temperature. Reducing the catalyst loading to 1 mol % gave a 78% yield of ;α-aminonitrile under identical reaction conditions (Table 1, entry 1). No cyanohydrin trimethylsilyl ether (from the ketone and trimethylsilyl cyanide) was detected, perhaps due to the rapid formation and activation of the imines by the $Fe(Cp)_2PF_6$ catalyst.

We extended our studies using a variety of aromatic and aliphatic ketones and different amines using $Fe(Cp)_2PF_6$ (5 mol %). The data in Table 2 shows that substituents on the aromatic ring of the ketone play a crucial role in product formation. A 4-substituted acetophenone with an electron-donating group ($-CH_3$) gave a higher conversion (Table 2, entry 4) than with an electron-withdrawing group (–F, NO_2) (entries 3 and 8). Furthermore, conducting the reaction with an *o*-substituted acetophenone such as 2-bromoacetophenone gave an 81% yield of α-aminonitrile within 20 min (Table 2, entry 5), and with 2-acetonaphthone and benzophenone, the former gave a good yield (88%) of α-aminonitrile and the latter 68% (Table 2, entries 9 and 10). When benzylamine was used in combination with acetophenone or propiophenone, good yields of the corresponding α-aminonitriles were obtained. Reaction of 2-chloroaniline with acetophenone gave a yield of 73% (Table 2, entry 11). Furthermore, reaction of an aliphatic ketone versus 3-methyl-2-butanone as a substrate with aniline and TMSCN gave a 78% yield of α-aminonitrile within 20 min (Table 2, entry 12).

The synthesis of α-aminonitriles was also investigated by the reaction of a variety of aromatic, aliphatic and heterocyclic aldehydes with various amines using $Fe(Cp)_2PF_6$ (5 mol %) under identical reaction conditions. 4-Substituted benzaldehydes with an electron-donating group (OCH_3, CH_3) gave poorer conversions (Table 3, entries 2 and 6) than those with electron-withdrawing groups (F, Cl) (entries 14 and 15). 2-Thiophene-carboxaldehyde and 2-furan-carboxaldehyde gave good yields (entries 3 and 4), while an α,β-unsaturated aldehyde gave a somewhat poorer yield (entry 5). Using benzylamine, yields varied from 65% to 93%.

Scheme 1 depicts a probable mechanism for the formation of α-aminonitriles, which is based on the fact that no cyanohydrin trimethylsilylether was detected. The amines used are better nucleophiles than trimethylsilylcyanide, hence, they react first with the carbonyl compound to



Scheme 1. Probable mechanism of the formation of α-aminonitriles.

produce the corresponding imine. The in situ generated imine was polarized by the catalyst making the imine carbon more prone to the attack by cyanide producing the TMS-derivative of the α-aminonitrile, which was readily hydrolyzed with water to give the product α-aminonitrile (Scheme 1).

In conclusion, we have developed a clean and environmentally friendly protocol for the one-pot synthesis of α-aminonitriles in up to 94% yields, from ketones/aldehydes in combination with an amine using readily available $Fe(Cp)_2PF_6$ as catalyst and TMSCN as cyanide source under solvent-free conditions.

Acknowledgements

N.H.K. thanks the DST and CSIR Network project on catalysis for financial assistance and also Dr. P. K. Ghosh, the Director of the Institute for providing instrumentation facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.136.

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