Tetrahedron Letters 60 (2019) 1434–1436

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic oxidative conversion of aldehydes into nitriles using $NH_3{\cdot}H_2O$/$FeCl_2$/NaI/$Na_2S_2O_8$: A practical approach to febuxostat

Han Chen [a], Sijia Sun [a], Haoying Xi [b], Kaifang Hu [b], Ning Zhang [b], Jingping Qu [a], Yuhan Zhou [a,*]

[a] *State Key Laboratory of Fine Chemicals, School of Pharmaceutical Science and Technology, Dalian University of Technology, Dalian 116024, China*
[b] *Merro Pharmaceutical Co., Ltd., Dalian 116036, China*

ARTICLE INFO

Article history:
Received 11 March 2019
Revised 20 April 2019
Accepted 25 April 2019
Available online 27 April 2019

Keywords:
Nitriles
Iron salt
Aqueous ammonia
Febuxostat

ABSTRACT

A novel approach to convert aldehydes into nitriles using $NH_3{\cdot}H_2O$/$FeCl_2$/NaI/$Na_2S_2O_8$ has been developed. Both alkyl and aryl nitriles were obtained in good to excellent yields. Electron-withdrawing and electron-donating groups, such as fluoro, chloro, bromo, nitro, ester, cyano, trifluoromethyl and alkoxy were tolerated. Notably, febuxostat and its intermediate, ethyl 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylate, were obtained in excellent yields.

Febuxostat (Fig. 1), chemical name 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, is a drug for the treatment of hyperuricemia gout, which exerts its effect by the highly selective inhibition of xanthine oxidoreductase, thereby reducing uric acid concentration in the body [1,2]. Several routes have been reported for the synthesis of febuxostat, and most of them include the introduction of a cyano group [3]. In general, the conversion of an aldehyde group to the corresponding cyano group is a key step in its industrial production.

Various methods have been reported for the conversion of the aldehydes to nitriles, which can be mainly classified into three categories depending on the ammonia source used.

In the first type, NH_2OH is used to convert the aldehyde group to an oxime group, and through subsequent dehydration, nitriles are obtained. Typical reaction systems include $NH_2OH{\cdot}HCl$/HCOOH/HCOONa [4], $NH_2OH{\cdot}HCl$/dry-CSMIL (chitosan supported magnetic ionic liquid)/$MeSO_2Cl$ [5], and $NH_2OH{\cdot}HCl$/Pyridine/$TiCl_4$ [6]. However, most of these reactions require the use of strong acids, highly toxic solvents, or harsh reaction conditions.

In the second type, HMDS (hexamethyldisilazane) is used as the nitrogen source in combination with TEMPO/KPF_6/$NaNO_2$/O_2 [7] or AcNH-TEMPO$^+BF_4^-$/Pyridine [8]. Although such reactions typically give good yields, the relatively high price of HMDS hinders its application.

In the third type, aldehydes are reacted with ammonia or an ammonium salt to form imines, which are then oxidized to generate nitriles. Various oxidants including $NaICl_2$ [9], S_8/$NaNO_2$ [10], NBS [11], IBX [12], H_5IO_6/KI [13], PTAB [14], I_2 [15,16] are efficient for this transformation. However, most of them are relatively expensive. On the other hand, using metallic salts as catalysts, some cheaper oxidants can be used. For example, $CuBr_2$/O_2/TEMPO [17], $K_2S_2O_8$/$NiSO_4$ [18] and H_2O_2/$CeCl_3{\cdot}7H_2O$ [19] have been documented. However, some metallic ions, for example Ni^{2+}, are harmful to the environment, and in some cases, the by-product carboxylic acids, were formed in considerable amounts [18]. Thus, an efficient and highly selective approach using inexpensive and environmental-friendly reagents is still desired.

Among the above mentioned systems which can convert an aldehyde group into a cyano group, NH_3/I_2 has been widely used for its high yields and mild reaction conditions [15,16]. However, its application in industry is hindered by the high price of I_2 which is consumed in stoichiometric amounts. Because I_2 is reduced to I^- in the reaction, we proposed to oxidize I^- to I_2 with cheaper oxidants, so that only a catalytic amount of iodine can be utilized.

Regarding the choice of catalyst, iron was considered due to its advantages which include low cost, low toxicity and environmental friendliness. The application of iron salts and their complexes [20] has been widely reported. In particular, the Fe/$Na_2S_2O_8$ system has proven to be efficient in various oxidation process [21,22]. Inspired by this, we attempted to develop an iodine cycle to oxidize the imines to nitriles using the Fe/$Na_2S_2O_8$ system.

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* Corresponding author.
E-mail address: zhouyh@dlut.edu.cn (Y. Zhou).

https://doi.org/10.1016/j.tetlet.2019.04.043
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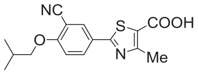


Fig. 1. Febuxostat.

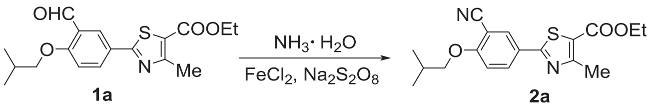
First, the febuxostat intermediate (**1a**) was chosen as a model substrate. In order to find a suitable iron salt, we initially examined the reaction using catalytic amounts of elemental iodine in ammonia water. When no oxidizing agent and iron salt were added, the reaction gave a poor yield (Table 1, entry 1). When 1.5 equivalents of $Na_2S_2O_8$ and different iron salts were added, the reaction yield was significantly improved (Table 1, entries 2–4). Among them, $FeCl_2$ worked best (Table 1, entry 2), and moderate conversion and yield were achieved. On this basis, different solvents were explored (Table 1, entries 5–8). To achieve higher conversion of the starting materials, the reaction temperature was raised from 40 °C to 50 °C. THF and 1,2-dichloroethane gave higher yields, and 1,2-dichloroethane was the best solvent choice (Table 1, entry 5).

Next, the amount of the iodine source and oxidant was studied. The experimental results showed that NaI was the best one (Table 2, entries 1, 6, and 8). When the amount of NaI (Table 2, entries 3–6) reached 5 mol%, the highest yield was obtained. When no $FeCl_2$ was added, the reaction gave a poor yield (Table 2, entry 7). After determining the amount of NaI, the amount of $Na_2S_2O_8$ was also optimized (Table 2, entries 6, 10–13). This revealed that 1.5 equivalents of $Na_2S_2O_8$ was the best choice (Table 2, entry 6).

When the reaction temperature increased from 30 °C to 50 °C, the yield increased significantly (Table 3, entries 1–3). Upon further increasing the temperature, the yield decreased (Table 3, entry 4) due to the evaporation of ammonia. The results also showed that 16 h was essential for reaction completion (Table 3, entries 5–8).

With the optimized reaction conditions in hand, we set out to examine a range of aldehydes (Table 4). First, 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid was used to obtain febuxostat in excellent yield (**2b**). Next, a series of aromatic, heterocyclic and aliphatic aldehydes were tested. Aryl aldehydes with electron-withdrawing groups, such as chloro, fluoro, bromo, nitro, cyano, and trifluoromethyl groups gave good to excellent yields (**2d**-**2i**, **2l**, and **2m**). Aryl aldehydes with electron-donating groups, such as methyl (**2j**), methoxy (**2k**) and dimethylamino (**2n**) also gave good yields. The low yield of anthraldehyde (**2q**) could be attributed to steric hindrance. It is noteworthy that dialdehyde-containing substrates, such as *o*-phthalaldehyde (**2p**), also gave good yields. To our delight, heterocyclic substrates, such as 4-pyridinecarboxaldehyde, 2-thiophenecarboxaldehyde and 2-furaldehyde were converted into the corresponding nitriles (**2s**-**u**). Alkyl aldehydes and α,β-unsaturated aldehydes also underwent the transformation (**2v** and **2w**).

Table 2
Optimization of the formation of **2a** based on [I] and oxidant amounts.[a]



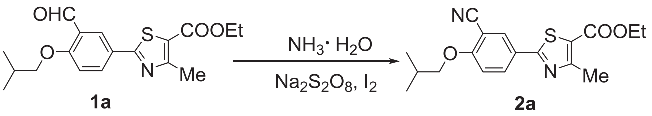
Entry	[I]	$Na_2S_2O_8$	Yield **2a** (%)[b]
1	KI (5 mol%)	1.5 eq.	91
2	KI (20 mol%)	1.5 eq.	99
3	–	1.5 eq.	22
4	NaI (1 mol%)	1.5 eq.	55
5	NaI (3 mol%)	1.5 eq.	92
6	NaI (5 mol%)	1.5 eq.	99
7[c]	NaI (5 mol%)	1.5 eq.	22
8	I_2 (2.5 mol%)	1.5 eq.	89
9	I_2 (5 mol%)	1.5 eq.	98
10	NaI (5 mol%)	–	28
11	NaI (5 mol%)	1.0 eq.	71
12	NaI (5 mol%)	1.2 eq.	84
13	NaI (5 mol%)	2.0 eq.	99

[a] Reagents and conditions: **1a** (1 mmol), $C_2H_4Cl_2$ (8 mL), $FeCl_2$ (10 mol%), 50 °C, $NH_3{\cdot}H_2O$ (3 mL).
[b] Yield was determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.
[c] no $FeCl_2$.

To further demonstrate the synthetic utility of the procedure, a gram-scale reaction of **1a** was conducted (20 mmol, Table 4, 2a). Compound **2a** (6.74 g) was obtained in 98% isolated yield, which was almost the same as that in the small scale reaction. This indicated that the $FeCl_2$/NaI-catalyzed oxidative cyanation of aldehydes can be readily scaled up to gram-scale, which is of significant benefit to industrial production.

During the reaction optimization, we observed that when NaI, $FeCl_2$, and $Na_2S_2O_8$ were absent (Table 1, entry 1), the reaction hardly occurred. When any one of them was absent (Table 2,

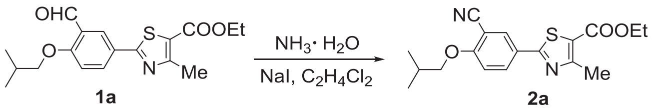
Table 1
Optimization of the formation of **2a** based on various ferric salts and solvents.[a]



Entry	[Fe]	Solvents	$Na_2S_2O_8$	T (°C)	Yield **2a** (%)[b]
1	–	CH_2Cl_2	–	40	12
2	$FeCl_2$	CH_2Cl_2	1.5 eq.	40	62
3	$FeCl_3$	CH_2Cl_2	1.5 eq.	40	42
4	Fe_2SO_4	CH_2Cl_2	1.5 eq.	40	40
5	$FeCl_2$	$C_2H_4Cl_2$	1.5 eq.	50	99
6	$FeCl_2$	Toluene	1.5 eq.	50	54
7	$FeCl_2$	MTBE	1.5 eq.	50	36
8	$FeCl_2$	THF	1.5 eq.	50	92

[a] Reagents and conditions: **1a** (1 mmol), solvent (8 mL), I_2 (10 mol%), $NH_3{\cdot}H_2O$ (3 mL).
[b] Yield was determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

Table 3
Optimization of the formation of **2a** based on temperature and reaction time.[a]

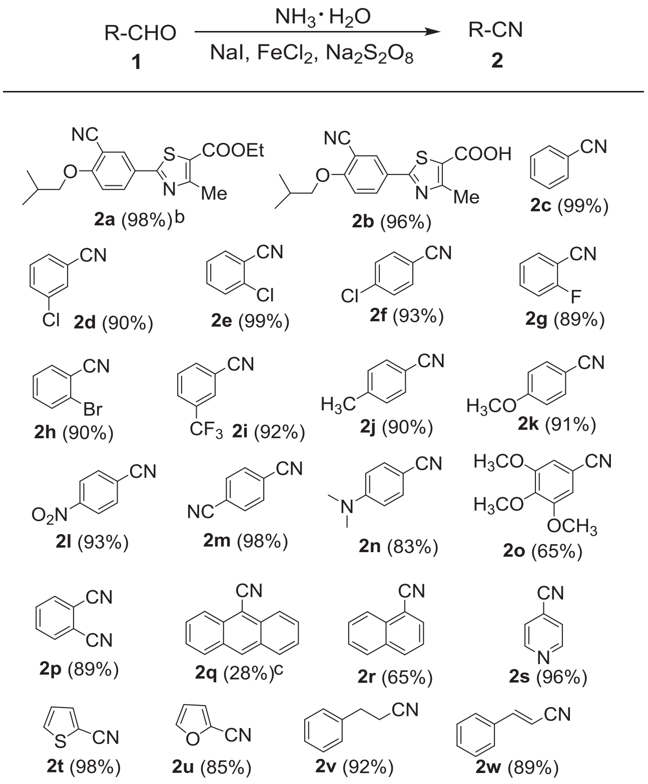


Entry	T (°C)	t (h)	Yield **2a** (%)[b]
1	30	18	78
2	40	18	85
3	50	18	99
4	60	18	81
5	50	9	83
6	50	12	89
7	50	16	99
8	50	24	99

[a] Reagents and conditions: **1a** (1 mmol), $C_2H_4Cl_2$ (8 mL), $FeCl_2$ (10 mol%), $Na_2S_2O_8$ (1.5 eq.), NaI (5 mol%), $NH_3·H_2O$ (3 mL).

[b] Yield was determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

Table 4
Preparation of nitrile derivatives.[a]

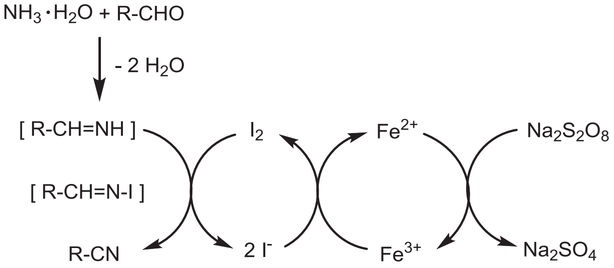


[a] Reagents and conditions: **1** (3 mmol), $C_2H_4Cl_2$ (10 mL), $FeCl_2$ (10 mol%), $Na_2S_2O_8$ (1.5 eq.), NaI (5 mol%), $NH_3·H_2O$ (9 mL), 50 °C, 16 h. Isolated yield.

[b] Reagents and conditions: **1a** (20 mmol), $C_2H_4Cl_2$ (60 mL), $FeCl_2$ (10 mol%), $Na_2S_2O_8$ (1.5 eq.), NaI (5 mol%), $NH_3·H_2O$ (60 mL), 50 °C, 16 h. Isolated yield.

[c] 70% of the starting material was recovered.

entries 3, 7, and 10), the yield was low. Based on these results, a reaction mechanism was proposed (Scheme 1). Initially, sodium persulfate oxidizes Fe^{2+} to Fe^{3+}, and then Fe^{3+} oxidizes I^- to form I_2. Next, I_2 oxidizes the imine intermediate which is obtained from the reaction of ammonia water and the aldehyde, thereby affording the corresponding nitrile product. At the same time, I_2 is reduced to I^- which participates in the oxidation of I^- to I_2 allowing the catalytic oxidation reaction to continue.



Scheme 1. Plausible reaction mechanism.

In conclusion, a novel method for the synthesis of nitriles from aldehydes has been developed. Using $NH_3·H_2O$ /$FeCl_2$/NaI/$Na_2S_2O_8$, various nitriles bearing either electron-withdrawing or electron-donating groups, such as fluoro, chloro, bromo, alkyl, and alkoxy, were obtained in good to excellent yields. Notably, the method was efficient for the preparation of febuxostat and its intermediate, ethyl 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methyl-5-thiazolecarboxylate.

Acknowledgments

The authors gratefully acknowledge the financial support of the National Natural Science Foundation of China (No. 21576041). We also thank Prof. Baomin Wang and Dr. Yuming Song for valuable discussions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.04.043. These data include MOL files and InChiKeys of the most important compounds described in this article.

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