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Zinc cyanide mediated direct α-cyanation of isonicotinic acid N-oxide. Application to the synthesis of FYX-051, a xanthine oxidoreductase inhibitor

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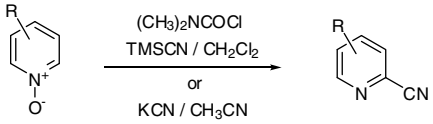
ABSTRACT

Reaction of isonicotinic acid N-oxide **1a** with dimethylcarbamoyl chloride and zinc cyanide in CH_3CN at 120 °C gave the corresponding 2-cyanoisonicotinamide **2a** in a good yield. This strategy was applied to the synthesis of FYX-051·TsOH **8**, a xanthine oxidoreductase inhibitor.

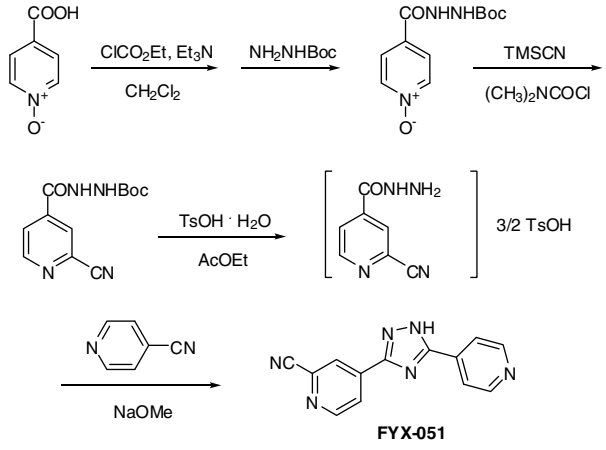
The synthesis of substituted cyanopyridines has been of considerable interest because the structural framework of cyanopyridines is often found in important biologically active compounds.[1] Cyanation of pyridine N-oxides is one of the most useful synthetic methods for the formation of cyano-substituted pyridines.[2] Efficient methods for the synthesis of various cyanopyridines and their derivatives from pyridine N-oxides have been developed. For example, the reaction of cyanide ions with pyridine N-oxides in the presence of an acylating agent[3] or with pyridine N-oxide quaternary salts provides the corresponding cyanopyridines in good yields.[4,5]



(1)

R = H; 2,3, or 4-Me; 3-CO_2Me; 3-CN; 3-Cl; 3-OMe

FYX-051, 4-(5-pyridin-4-yl-1*H*-[1,2,4]triazol-3-yl)pyridine-2-carbonitrile,[6] is a new xanthine oxidoreductase (XOR) inhibitor developed by Fuji Yakuhin Co., Ltd XOR catalyzes the last two reactions of purine catabolism, that is, the hydroxylation of hypoxanthine to xanthine and of xanthine to uric acid. FYX-051 was synthesized by Fukuzyu pharmaceuticals Co., Ltd (Toyama, Japan) according to the reaction sequence shown in Scheme 1.



Scheme 1.

First, commercially available isonicotinic acid N-oxide was protected by Boc-hydrazine, and the resulting protected pyridine N-oxide was treated with expensive TMSCN in the presence of $(CH_3)_2NCOCl$, giving the α-cyanopyridine derivative in 69% yield. Then, deprotection of the Boc group was needed before condensation with *para*-cyanopyridine (Scheme 1). It would be advantageous to avoid the protection–deprotection steps and also to avoid the use of expensive TMSCN. Therefore, development of a new method for direct cyanation from isonicotinic acid N-oxide

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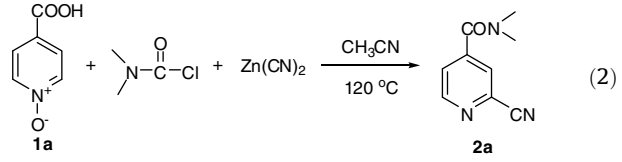
Table 1
Effect of cyanide sources and solvents on the formation of 2-cyanoisonicotinamide **2a** from **1a**[a]

Entry	Cyanide source	Solvent	Yield of **2a**[b] (%)
1	$Zn(CN)_2$	CH_3CN	69 (66)[c]
2	AgCN	CH_3CN	42
3	$Hg(CN)_2$	CH_3CN	37
4	KCN	CH_3CN	35
5	CuCN	CH_3CN	nr[d]
6	$Zn(CN)_2$	THF	15
7	$Zn(CN)_2$	DMF	32
8	$Zn(CN)_2$	1,4-Dioxane	(42)
9	$Zn(CN)_2$	AcOEt	43 (43)
10	$Zn(CN)_2$	Toluene	52 (47)
11	$Zn(CN)_2$	CH_3CN	(66)[e]
12	$Zn(CN)_2$	CH_3CN	62 (58)[f]
13	$Zn(CN)_2$	CH_3CN	67 (66)[g]

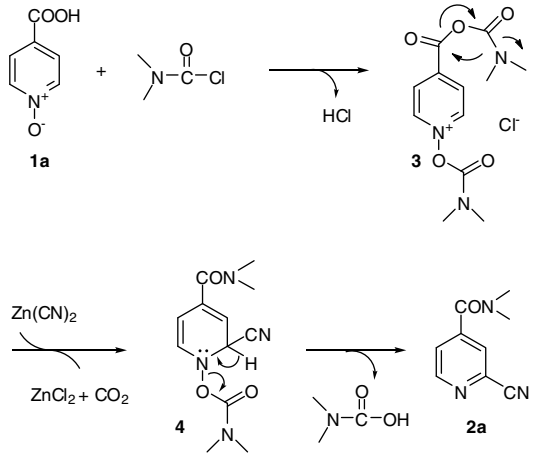
[a] The reaction of **1a** with a cyanating agent (1.5 equiv $Zn(CN)_2$ or 3 equiv KCN, CuCN, and AgCN) was carried out in the presence of 3 equiv of dimethylcarbamoyl chloride at 120 °C for 12 h.
[b] ^1H NMR yield using dibromomethane as an internal standard. Isolated yield is shown in parentheses.
[c] Reaction time was 5 h.
[d] Starting material was recovered.
[e] 2 equiv of dimethylcarbamoyl chloride were used.
[f] 1 equiv of $Zn(CN)_2$ was used.
[g] Reaction temperature was 100 °C.

using a cheap cyanation reagent was needed. Herein, we report a convenient, direct and one-step synthesis of 2-cyanoisonicotinamide **2a** from isonicotinic acid N-oxide **1a** using zinc cyanide (1.5 equiv) in the presence of dimethylcarbamoyl chloride (2 equiv) in CH_3CN at 120 °C (Eq. 2). Furthermore, this newly developed method was successfully applied for the synthesis of FYX-051·TsOH **8** (vide infra).



(2)

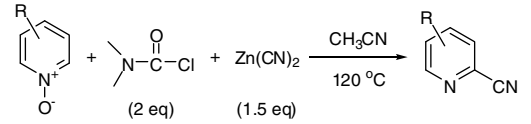
Initially, we examined the cyanation of isonicotinic acid N-oxide **1a** with various cyanides in the presence of dimethylcarbamoyl chloride (Table 1).[7] Among the cyanating agents we tested, $Zn(CN)_2$ gave the best result in CH_3CN (entry 1). No product was detected in the presence of CuCN (entry 5), and use of other cyanide sources such as AgCN, $Hg(CN)_2$, and KCN afforded **2a** in moderate yields (entries 2–4). Other solvents such as THF, DMF, 1,4-dioxane, ethyl acetate, and toluene, instead of acetonitrile, gave the product in lower yields (entries 6–10). Decreasing the amount of dimethylcarbamoyl chloride and zinc cyanide did not exert a strong influence on the product yield (entries 11 and 12). A decrease in the reaction temperature to 100 °C also did not affect the product yield (entry 13).



Scheme 2. A plausible mechanism for the formation of **2a**.

Next, we investigated the effect of acylating agents, and the results are summarized in Table 2. Dimethylcarbamoyl chloride was found to be the best acylating agent. The product **2a** was isolated in 66% yield when the reaction was carried out at 120 °C for 5 h in the presence of 3 equiv of dimethylcarbamoyl chloride (entry 1). The use of benzoyl chloride and lithium chloride did not lead to any product formation (entries 2 and 3).

A plausible mechanism for the $Zn(CN)_2$ mediated synthesis of 2-cyanoisonicotinamide **2a** is illustrated in Scheme 2. At the initial stage of the reaction, the intermediate 1-acyloxypyridinium ion **3** is formed as mentioned in previous literature.[2,3d,4b,5] The α-cyanation through reaction of **3** with $Zn(CN)_2$ and elimination of carbon dioxide afford the intermediate **4**. Removal of *N*,*N*-dimethylcarbamic acid from **4** gives 2-cyanoisonicotinamide **2a**.

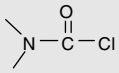
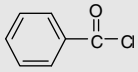


(3)

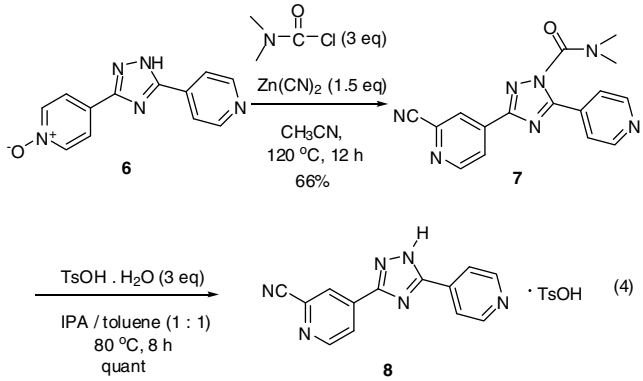
1b, R = H — **2b**, 67% (3 h)
1c, R = 4-CN — **2c**, 62% (8 h)

Thus, direct α-cyanation of the pyridine N-oxide **1a** substituted with a carboxylic acid has been achieved using cheap $Zn(CN)_2$. To determine the applicability of this new method, we examined

Table 2
Effect of acylating agents on the formation of 2-cyanoisonicotinamide **2a** from **1a**[a]

Entry	Acylating agent	Time (h)	Yield of **2a**, %[b]
1		5	69 (66)
2		12	nr[c]
3	LiCl	12	nr[c]

[a] The reaction of **1a** with $Zn(CN)_2$ (1.5 equiv) was carried out in the presence of 3 equiv of acylating agent at 120 °C in CH_3CN.
[b] ^1H NMR yield using dibromomethane as an internal standard. Isolated yield is shown in parentheses.
[c] Starting material was recovered.



(4)

Scheme 3.

the reactions of **1b** and **1c**. The α-cyanation of pyridine N-oxide (**1b**) and 4-cyanopyridine N-oxide (**1c**) proceeded very smoothly, giving the desired products **2b** and **2c** in good yields under the reaction conditions described previously (Eq. 3). Next, we applied this new method for an alternative synthesis of FYX-051 (Scheme 3). The pyridine N-oxide **6** substituted with a triazole group at the *para*-position was obtained easily via reaction of 4-cyanopyridine N-oxide with isonicotinic hydrazide, which was commercially available. The reaction of **6** with 1.5 equiv of $Zn(CN)_2$ and 3 equiv of $(CH_3)_2NCOCl$ in CH_3CN at 120 °C for 12 h gave the corresponding α-cyanation product **7** in 66% yield.[8] Deprotection of the N-carbamoyl group was carried out with 3 equiv of $TsOH{\cdot}H_2O$, giving FYX-051·TsOH **8** in quantitative yield (Eq. 4).[9]

In conclusion, we have reported a convenient method for the direct synthesis of 2-cyanoisonicotinamide from isonicotinic acid N-oxide using zinc cyanide as a cyanation reagent. Furthermore, this strategy was applied to the synthesis of FYX-051·TsOH, a xanthine oxidoreductase inhibitor.

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7. *The procedure for the synthesis of 2-cyanoisonicotinamide* **2a** *is as follows*: To a 5 mL screw capped vial equipped with a magnetic stirring bar were added isonicotinic acid N-oxide (27.8 mg, 0.2 mmol), dimethylcarbamoyl chloride (0.04 mL, 0.4 mmol), zinc cyanide (35.2 mg, 0.3 mmol), and acetonitrile (2 mL) under an argon atmosphere. The reaction mixture was stirred at 120 °C for 5 h, and the progress of the reaction was monitored by TLC (hexane/ethyl acetate; 1/1). After complete consumption of the starting material, the reaction mixture was cooled to room temperature and water was added, and stirring was continued for 5–15 min. The organic layer was separated, and the aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined ethyl acetate layers were dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate; 5/11/1) to afford product **2a** in 66% yield. (23.1 mg). Mp: 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 (3H, s), 3.14 (3H, s), 7.52 (1H, d, J = 5.0 Hz), 7.71 (1H, s), 8.80 (1H, d, J = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 35.07, 38.93, 116.42, 124.28, 126.04, 133.94, 145.01, 151.29, 166.49; IR (KBr) 3291, 2240, 1698, 1632, 1385, 880 cm^{-1}; HRMS (EI) calcd for $C_9H_9N_3O$ ([M+Na]$^+$) 198.0638, found 198.0637.
8. *Data for* **7**: Mp: 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.17 (3H, s), 3.29 (3H, s), 8.07–7.99 (3H, m), 8.21 (1H, m), 8.78 (2H, d, J = 5.0 Hz), 8.89 (1H, d, J = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 37.83, 39.28, 120.74, 125.32, 127.12, 132.08, 134.70, 135.73, 136.66, 150.02, 150.55, 151.76, 153.37, 160.14; IR (KBr) 2921, 2242, 1716, 1605, 1456, 1091, 836, 749 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{13}N_7O$ ([M+H]$^+$) 320.1254, found 320.1253.
9. *The procedure for the synthesis of FYX-051·TsOH* **8** *from* **7** *is as follows*: To a 5 mL screw capped vial equipped with a magnetic stirring bar were added compound **7** (63.8 mg, 0.2 mmol), $TsOH{\cdot}H_2O$ (114.1 mg, 0.6 mmol), and IPA/toluene (1/1, 1.4 mL). The reaction mixture was stirred at 80 °C for 8 h, and the progress of the reaction was monitored by TLC (ethyl acetate). After complete consumption of the starting material, the solvents were removed under reduced pressure, the residue was washed three times with ethyl acetate (3 mL), and the solid product obtained was dried to afford FYX-051·TsOH **8** in quantitative yield as a white solid (84.0 mg). Mp: 236–238 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.27 (3H, s), 7.10 (2H, d, J = 8.0 Hz), 7.45 (2H, d, J = 8.0 Hz), 8.57–8.27 (4H, m), 8.98–8.91 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6): 20.87, 117.08, 122.87, 122.88, 123.82, 125.18, 125.19, 125.61, 128.39, 133.65, 133.66, 136.04, 138.37, 143.70, 144.80, 152.48. HRMS (EI) calcd for $C_{13}H_8N_6$ ([M–TsOH+H]$^+$) 249.0883, found 249.0884.