Short communication

The Direct Formation of 2-Cyano-4-amidopyridine *via* α-Cyanation of 4-Amidopyridine *N*-Oxide with Dimethylcarbamoyl Chloride and Cheap Potassium Cyanide

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

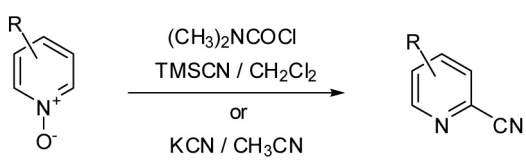
Abstract

Reaction of 4-amidopyridine *N*-oxide with dimethylcarbamoyl chloride and potassium cyanide in CH_3CN at 120 °C gave the corresponding 2-cyano-4-amidopyridine in a good yield.

Keywords: Potassium cyanide, α-cyanation, pyridine *N*-oxide, 2-cyano-4-amido pyridine, 4-amidopyridine *N*-oxide.

1. Introduction

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*-oxide is one of the most useful synthetic methods for the formation of cyano-pyridines.[2] Due to their potential importance, several synthetic methods from substituted 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 (Eq. 1).[4,5]



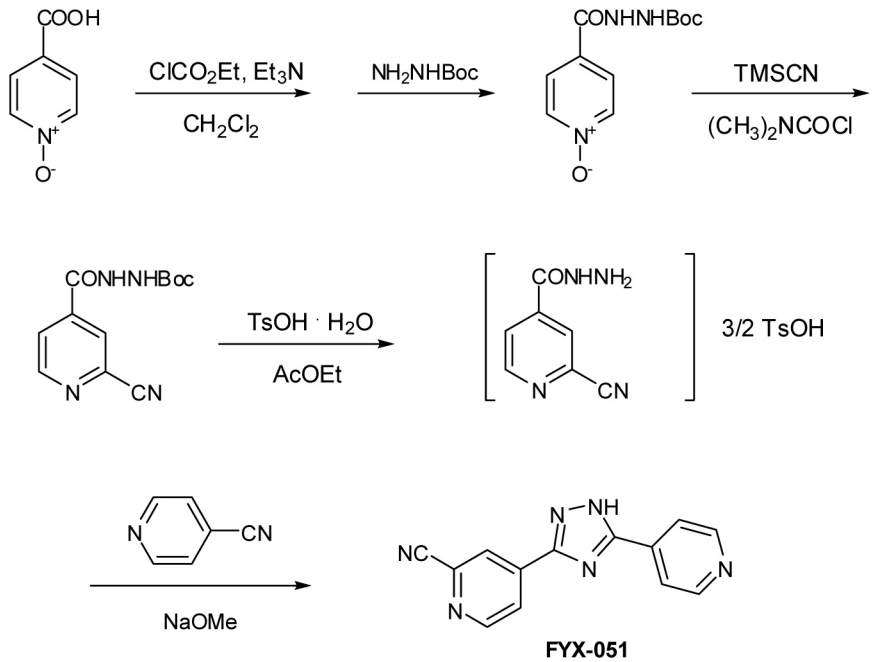
(1)

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, *i.e.* 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. 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 4-amidopyridine *N*-oxide **3** using a cheap cyanation reagent was needed.

2. Results and Discussion

Recently, we reported an convenient method for the direct synthesis of 2-cyanoisonicotinamide **2** from isonicotinic acid *N*-oxide **1** using zinc cyanide as a cyanation

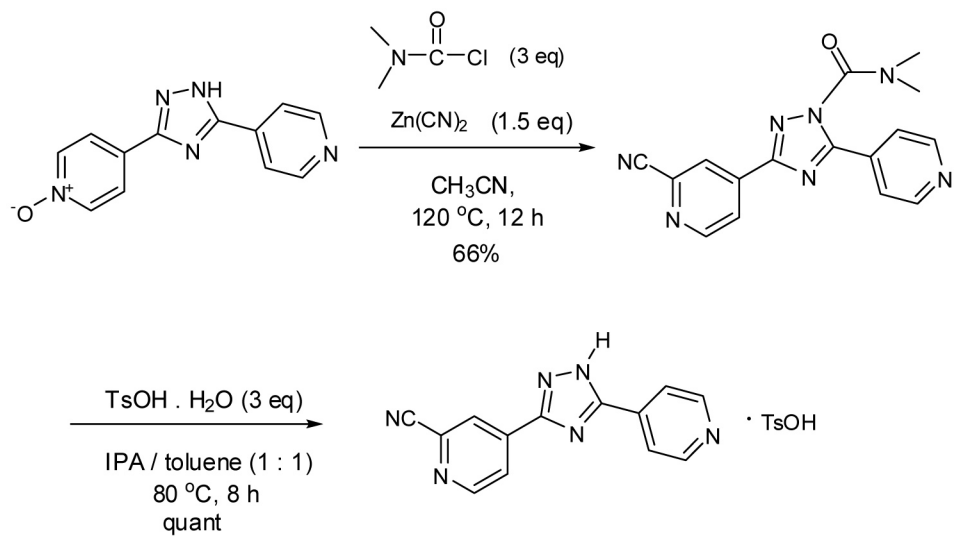


Scheme 1

reagent (Eq. 2).[7] This finding enabled the synthesis of FYX-051 · TsOH from the pyridine *N*-oxide using cheap cyanation reagent, $Zn(CN)_2$ (Scheme 2).[7] Encouraged by this finding, we thought that 4-amidopyridine *N*-oxide **3** would be converted to the corresponding α–cyanopyridine **4** using $Zn(CN)_2$ (Eq. 3). However, the reaction of **3** with $Zn(CN)_2$ and dimethylcarbamoyl chloride gave **4** in a low yield (Table 1, entry 4). Accordingly, it is clear that $Zn(CN)_2$ is not applicable to the α–cyanation of 4-amidopyridine *N*-oxides although it gave a good result in the case of isonicotinic acid *N*-oxide **1**.

We examined the cyanation of 4-amidopyridine *N*-oxide **3** with various cyanides and acylating agents (Eq 4, Table 1).[8] Dimethylcarbamoyl chloride was found to be the best acylating agent among the cyanating agents we tested, and KCN gave the best result in CH_3CN (entry 1). Use of other cyanide sources such as NaCN, AgCN and $Zn(CN)_2$ afforded product **4** in lower yields (entries 2–4), and no products was detected in the presence of CuCN and $Hg(CN)_2$ (entries 5 and 6). The use of benzoyl chloride and lithium chloride did not lead to any product formation (entries 7–9).

As shown in Figure 1, the time profile of the reaction of **3**, monitored by NMR, indicated that the starting substrate **3** was consumed completely within 4 h. However, the formation of **4** reached to plateau after 2.5 h and the yield (60%) did not increase significantly even at a prolonged reaction time. The reason why the curve of de-



Scheme 2

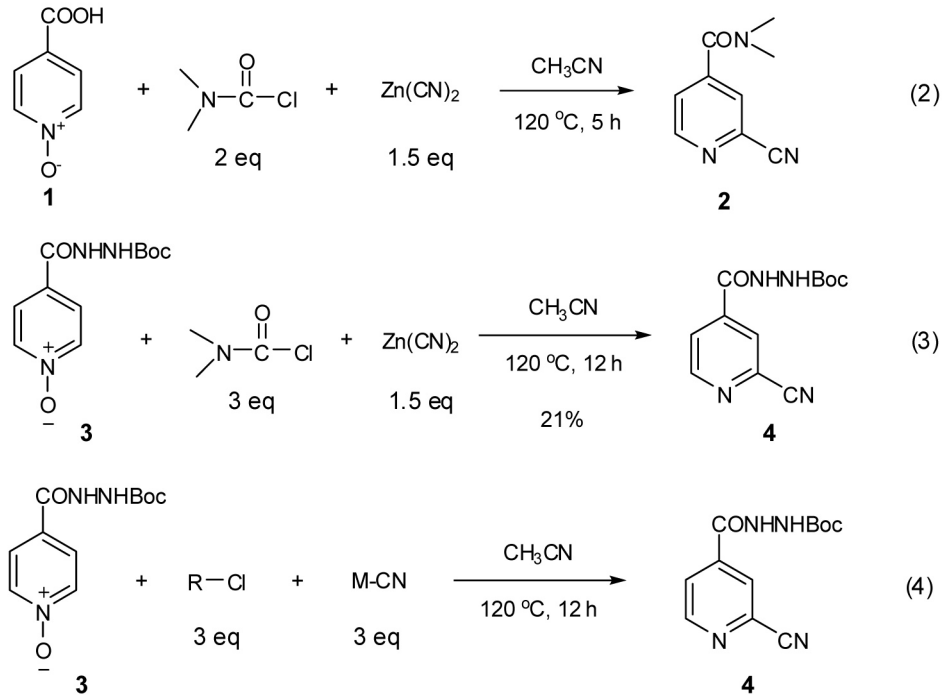
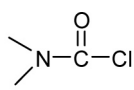
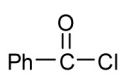


Table 1. Effect of cyanide sources and acylating agents on the formation of 2-cyano-4-amidopyridine **4** from **3**.[a]

entry	acylating agent	cyanide source	yield of 4, %[b]
1		KCN	64[c]
2		NaCN	20
3		AgCN	49
4		$Zn(CN)_2$	21[d]
5		CuCN	–[e]
6		$Hg(CN)_2$	–[d,e]
7		KCN	nr[f]
8		$Zn(CN)_2$	nr[d,f]
9	LiCl	KCN	nr[f]

[a] The reaction of **3** with a cyanating agent was carried out in the presence of 3 equiv of acylating agent in CH_3CN at 120 °C for 12 h. [b] Isolated yields. [c] Reaction time was 4 h. [d] 1.5 equiv of $Zn(CN)_2$ and $Hg(CN)_2$ were used. [e] Starting material decomposed. [f] Starting material was recovered

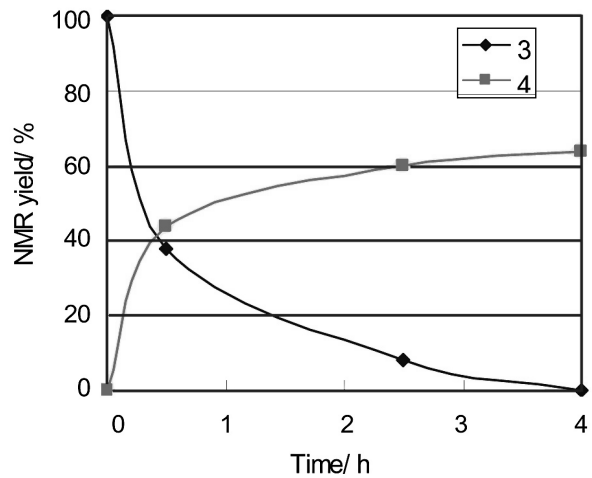


Figure 1. Time profile of the cyanation of **3** (0.1 mmol) in the presence of 3 eq dimethylcarbamoyl chloride and 3 eq KCN in CH_3CN at 120 °C.

crease of the starting material does not correspond well to that of increase of product formation is not clear.

Next, we investigated the effect of solvents, reaction temperature and amount of cyanides and acylating agents, and the results are summarized in Table 2. CH_3CN and THF gave the product in good yields (entries 1 and 2). Use of DMF, CH_2Cl_2, 1,4-dioxane, and AcOEt, instead of CH_3CN, gave the product in lower yields (entries 3–6). Other solvents such as H_2O, mixture of CH_3CN and H_2O, toluene, DMSO and Et_2O were inefficient and no desired product was obtained (entries 7–11). Decreasing the amount of dimethylcarbamoyl chloride gave a low yield (entry 12). The product **4** was isolated in 64% yield when the reaction was carried out at 120 °C for 4 h in the presence of 2 equiv of potassium cyanide (entry 13). Decrease of reaction temperature from 120 °C to 100 °C did not affect the product yield (entry 15).

A plausible mechanism for the KCN mediated synthesis of 2-cyano-4-amidopyridine **4** is illustrated in Scheme 2. At the initial stage of the reaction, the intermediate 1-acyloxypyridinium ion **A** is formed as mentioned in the previous literatures.[2,3d,4b,5] The α–cyanation through

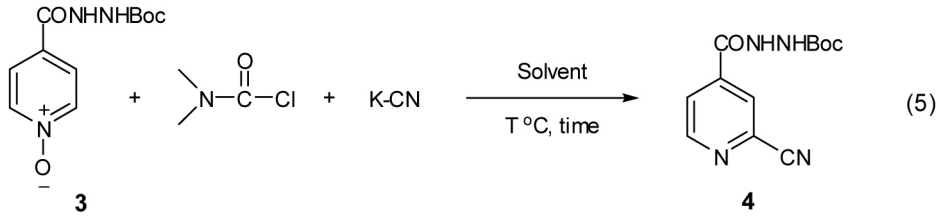
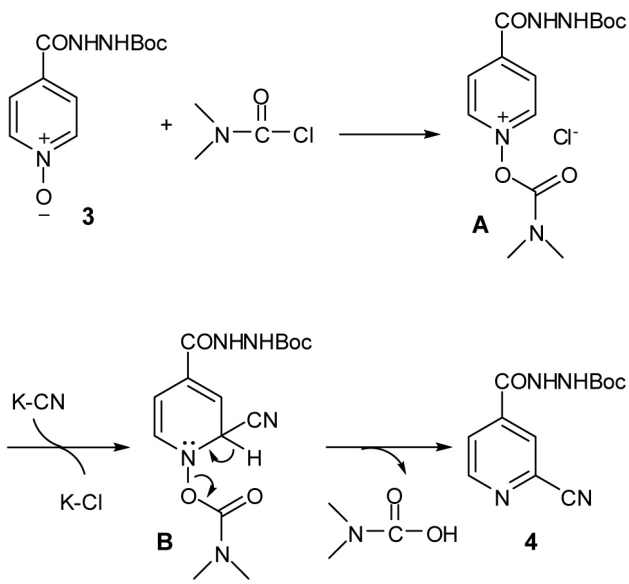


Table 2. Effect of solvents, amount of cyanide sources and acylating agents and temperature on the formation of 2-cyano-4-amidopyridine **4** from **3**.[a]

entry	solvent	acylating agent (eq)	cyanide source (eq)	temp (°C)	time (h)	yield of 4, %[b]
1	CH_3CN	3	3	120	4	64
2	THF	3	3	120	12	61
3	DMF	3	3	120	12	37[c]
4	CH_2Cl_2	3	3	120	12	15[c]
5	1,4-dioxane	3	3	120	12	20[c]
6	AcOEt	3	3	120	12	13[c]
7	H_2O	3	3	120	12	nr
8	$CH_3CN + H_2O$	3	3	120	12	nr
9	Toluene	3	3	120	12	nr
10	DMSO	3	3	120	12	nr
11	Et_2O	3	3	120	12	nr
12	CH_3CN	2	3	120	24	37[c,d]
13	CH_3CN	3	2	120	4	64
14	CH_3CN	3	1	120	24	47[c,e]
15	CH_3CN	3	2	100	7	64
16	CH_3CN	3	3	70	24	25[c,f]

[a] The reaction of **3** with 3 equiv of cyanating agent was carried out in the presence of 3 equiv of acylating agent inCH_3CN at 120 °C. [b] Isolated yields. [c] 1H NMRyield using *p*-xylene as an internal standard. [d] 15% of **3** was recovered. [e] 10% of **3** was recovered. [f] 35% of **3** was recovered.

the reaction of **A** with KCN affords the intermediate **B**. Removal of *N,N*-dimethylcarbamic acid from **B** gives 2-cyano-4-amidopyridine **4**.



3. Conclusion

We have developed an efficient method for the direct formation of 2-cyano-4-amidopyridine from 4-amidopyridine *N*-oxide using cheap potassium cyanide as a cyanating agent.

4. References

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8. The procedure for the synthesis of 2-cyano-4-amidopyridine **4** is as follows. To a 5 mL screw capped vial equipped with a magnetic stirring bar were added 4-amidopyridine *N*-oxide (50.6 mg, 0.2 mmol), dimethylcarbamoyl chloride (0.056 mL, 0.6 mmol), potassium cyanide (26.0 mg, 0.4 mmol), and acetonitrile (2 mL) under an argon atmosphere. The reaction mixture was stirred at 120 °C for 4 h, and the progress of the reaction was monitored by TLC (hexane/ethyl acetate; 2/1). 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 minutes. 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; 10/1 ~2/1) to afford product **4** in 64% yield. (33.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s), 7.86 (1H, d, J = 5.0 Hz), 8.07 (1H, s), 8.88 (1H, d, J = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 26.85, 48.54, 80.65, 116.08, 121.90, 124.54, 125.97, 133.84, 141.27, 151.50; IR (KBr) 2980, 2239, 1706, 1666, 1364, 1156, 762 cm^{-1}; HRMS (EI) Calcd for $C_{12}H_{14}N_4O_3$ ([M+Na]$^+$) 285.0958. Found 285.0958.

Povzetek

Opisana je reakcija 4-amidopiridin *N*-oksida z dimetilkarbamoil kloridom in kalijevim cianidom v acetonitrilu pri 120 °C, ki je vodila do ustreznega 2-ciano-4-amidopiridina z dobrim iskoristkom.