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SYNTHESIS AND REACTIONS OF 4-CHLORO-1,2-DIHYDRO-6-METHYL-2-OXO-3-PYRIDINECARBONITRILE

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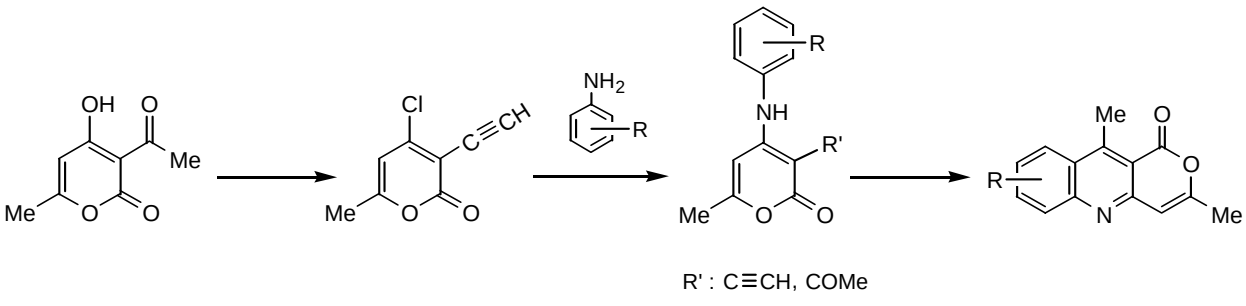
Abstract – The chlorination of 1,2-dihydro-4-hydroxy-6-methyl-2-oxo-3-pyridinecarbonitrile (**2**) with a mixture of $POCl_3$ and PCl_5 in $CHCl_3$ gave 4-chloro-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (**3**) in good yield. Compound (**3**) reacted with alkyl- and arylamines to give the corresponding 4-alkylamino- and 4-arylamino-3-pyridinecarbonitriles (**6** and **7**).

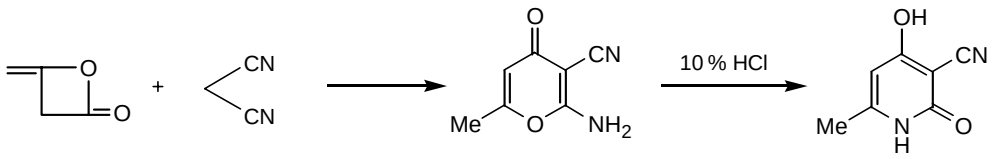
We previously reported new synthetic methods for the pyrano[4,3-*b*]quinoline derivatives by the cyclization of 4-arylamino-3-ethynyl-2-pyrones[1] or 3-acetyl-4-arylamino-2-pyrones[2] as shown in Scheme 1. It is considered that these methods are also available for the synthesis of the acridine analogues, which have attracted interest as memory-enhancing agents for the treatment of Alzheimer's disease.[3]



Scheme 1

During the course of our investigation on the synthesis of the pyrane-fused heterocycles, we found that 4-chloro-3-pyridinecarbonitrile (**3**) was obtained by the chlorination of 4-hydroxy-2-pyridone-3-carbonitrile (**2**). We believe that the compound (**3**), like 4-chloro-3-ethynyl-2-pyrone in Scheme 1, could be used as a starting material for the synthesis of the acridine analogues. In order to explore this aspect, we examined the efficient synthetic method of 4-chloro-3-pyridinecarbonitrile (**3**) and the reaction of **3** with amines.

First, we describe the preparation of 4-chloro-3-pyridinecarbonitrile (**3**). Kato and his co-workers reported [4] that 4-hydroxy-2-oxo-3-pyridinecarbonitrile (**2**) was obtained in 75 % yield by the ring transformation of 2-amino-6-methyl-4-oxo-4*H*-pyran-3-carbonitrile (**1**), which was prepared from diketene and malononitrile, in ethanol saturated with hydrogen chloride. However, it was proved that this ring transformation also smoothly proceeded under acidic aqueous conditions. Thus, a suspension of **1** (30 g) in 10 % HCl (400 mL) was heated under reflux for 4 h to give **2** in 87 % yield.



1 **2**

Scheme 2

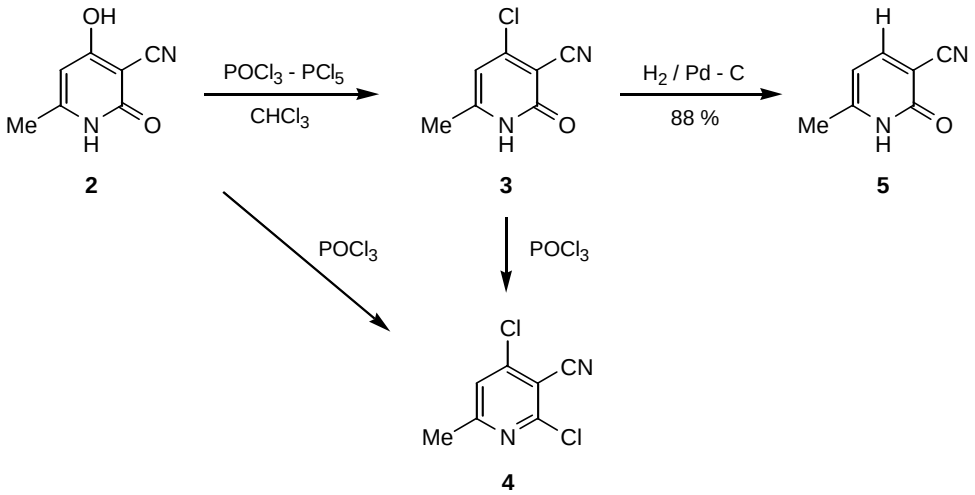
As a general method for the preparation of halopyridinecarbonitriles, the reaction of the hydroxy-pyridinecarbonitriles or hydroxypyridinecarboxamides with $POCl_3$ or PCl_5 is well known.[5-7] Furthermore, there are a few reports that the chlorination of the 4-hydroxy-2-pyridone derivatives, which have the same substructure with **2**, with $POCl_3$ does not produce the monochlorinated product but 2,4-dichloro-6-methyl-3-pyridinecarbonitrile (**4**).[8-10] 4-Chloro-3-pyridinecarbonitrile (**3**) as the expected product in this chlorination has three types of functional group such as the chloro, nitrile and amide groups, and it has been considered for use as a potential compound in the synthesis of heterocycles.

We tried to obtain **3** under various conditions and these results of the chlorination are shown in Table 1. For the chlorination of **2**, $POCl_3$ and PCl_5 were used because they are inexpensive and easy to obtain.

Table 1. Chlorination Conditions for **2**

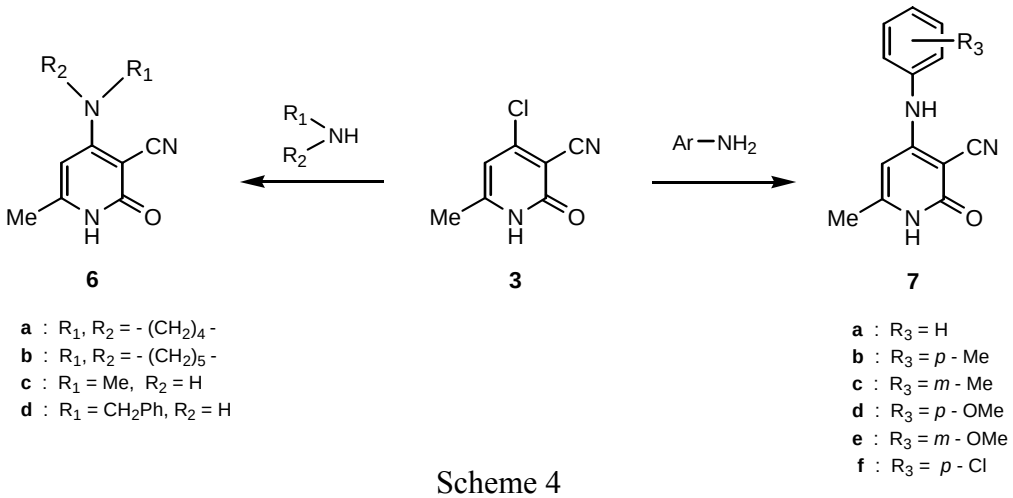
Run	Reagent (mol eq.)		Solvent	Yield (%)	
	$POCl_3$	PCl_5		**3**	**4**
1	5	—	—	trace	75
2	2.5	—	$CHCl_3$	1.5	—
3	—	2.5	$CHCl_3$	27	—
4	2	2	$CHCl_3$	75	2

The chlorination of **2** with $POCl_3$ gave **4** in 75 % yield with only a trace of the monochloro compound (**3**) (Run 1). Using both $POCl_3$ (Run 2) and PCl_5 (Run 3) in $CHCl_3$ resulted in producing **3** in low yield as shown in Table 1. However, the important point is that the use of a mixture of $POCl_3$ and PCl_5 in $CHCl_3$ selectively gave the 4-chloro-3-pyridinecarbonitrile (**3**) (Run 4). Thus, a mixture of **2**, $POCl_3$ (2 mol eq.), and PCl_5 (2 mol eq.) in $CHCl_3$ was heated under reflux to give 4-chloro-3-pyridinecarbonitrile (**3**) in 75 % yield. The position of the chlorine atom in **3** was determined by converting **3** into 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (**5**) by catalytic hydrogenolysis. The ^{1}H-NMR spectrum of the reduced product (**5**) shows the two typical signals of the *ortho*-coupled protons at 6.21 ppm and 8.01 ppm that arise from the 5- and 4-positions, and the melting point of **5** agrees well with the previous data.[11] Though it is natural, the chlorination of **3** with $POCl_3$ was smoothly carried out to give **4** in almost quantitative yield.



Scheme 3

Next, we investigated the reactions of **3** with alkylamines and arylamines. Thus, a mixture of **3** and pyrrolidine (2.5 mol eq.) in MeOH was heated under reflux for 1 h to give a product (**6a**) in 93 % yield. The structure of **6a** was based on the analytical and spectral data which are shown in Table 2. Namely, the molecular formula of **6a** is $C_{11}H_{13}N_3O$. In the IR spectrum (KBr) of **6a**, the characteristic absorption of the -CN function appeared at 2210 cm^{-1} and the C=O absorption of the amide group is observed at 1650 cm^{-1}, and furthermore, the ^{1}H-NMR spectrum shows peaks of olefin and methyl protons as singlets at 6.31 and 2.47 ppm, respectively, and of the pyrrolidine ring protons as multiplets at 2.02-2.33 and 3.67-4.15 ppm. These data support the fact that **6a** is 1,2-dihydro-6-methyl-2-oxo-4-(pyrrolidin-1-yl)-3-pyridinecarbonitrile. In a similar fashion, the use of piperidine, methylamine, and benzylamine gave the corresponding products (**6b**, **6c**, and **6d**), respectively.



6

a : $R_1, R_2 = -(CH_2)_4-$
b : $R_1, R_2 = -(CH_2)_5-$
c : R_1 = Me, R_2 = H
d : $R_1 = CH_2Ph$, R_2 = H

3

7

a : R_3 = H
b : R_3 = *p* - Me
c : R_3 = *m* - Me
d : R_3 = *p* - OMe
e : R_3 = *m* - OMe
f : R_3 = *p* - Cl

Scheme 4

On the other hand, when using arylamines instead of alkylamines, the reaction time had to be extended in order to get the corresponding 4-arylamino-3-pyridinecarbonitriles (**7a-f**) in satisfactory yield. For example, the heating of a mixture of **3** and aniline in MeOH for 20 h afforded 4-phenylamino-3-pyridinecarbonitrile (**7a**) in 90 % yield. In these reactions, because the nucleophilicity of the arylamines decreased, it needed an extended reaction time. The structures of the products (**7a-f**) were confirmed by the spectral and analytical evidence shown in Table 2.

These results provided methods of synthesizing 4-chloro-3-pyridinecarbonitrile (**3**) and the 4-alkylamino- and 4-arylamino-3-pyridinecarbonitrile derivatives (**6** and **7**). Especially, the substituted pyridines are an important biologically active products. As demonstrated in these transformations, 4-chloro-3-pyridinecarbonitrile (**3**) serves as a potential intermediate for a variety of substituted pyridines.

Table 2. Reaction of **3** with amines

Amine	Reflux (h)	Product No.	Yield(%) (Solvent)	mp (°C)	Formula (*m/z* M^+)	*Anal.* (%) Calcd (Found) C	H	N	IR[KBr] (cm^{-1})	^{1}H-NMR δ(ppm)
pyrrolidine	1	**6a**	93 (MeOH)	343-345 (decomp)	$C_{11}H_{13}N_3O$ (203)	65.01 (64.92	6.45 6.45	20.68 20.67)	2210, 1650, 1610	2.02-2.33 (m, 4H), 2.47 (s, 3H), 3.67-4.15 (m, 4H), 6.31(s, 1H) [CF_3COOD]
piperidine	1	**6b**	87 (AcOEt)	267-268 (decomp)	$C_{12}H_{15}N_3O$ (217)	66.34 (66.55	6.96 6.99	19.34 19.50)	2210, 1630	1.71 (br s, 6H), 2.31 (s, 3H), 3.62 (br s, 4H), 5.71 (s, 1H), 12.57 (br s, 1H) [$CDCl_3$]
methylamine	1	**6c**	71 (MeOH)	290-291 (decomp)	$C_8H_9N_3O$ (163)	58.88 (58.59	5.56 5.90	25.75 25.73)	3350, 2220, 1620	2.12 (s, 3H), 2.83 (d, *J*=4.6 Hz, 3H), 5.71 (s, 1H), 7.04 (br, 1H),10.99 (br, 1H) [DMSO]
benzylamine	1	**6d**	89 (MeOH)	317-318 (decomp)	$C_{14}H_{13}N_3O$ (239)	70.28 (70.38	5.48 5.49	17.56 17.67)	3300, 2215, 1625	2.36 (s, 3H), 4.61 (s, 2H), 6.09 (s, 1H), 7.36 (s, 5H) [$CDCl_3$ - CF_3COOD]
aniline	20	**7a**	90 (EtOH)	290 (decomp)	$C_{13}H_{11}N_3O$ (225)	69.32 (69.04	4.92 5.00	18.66 18.51)	3250, 2220, 1670, 1630	2.30 (s, 3H), 6.05 (s, 1H), 7.16-7.57 (m, 5H) [$CDCl_3$ - CF_3COOD]
p-toluidine	5	**7b**	89 (EtOH)	325-326 (decomp)	$C_{14}H_{13}N_3O$ (239)	70.28 (70.56	5.48 5.40	17.56 17.64)	3280, 2215, 1625	2.27 (s, 3H), 2.40 (s, 3H), 5.97 (s, 1H), 7.00-7.76 (m, 4H) [$CDCl_3$ - CF_3COOD]
m-toluidine	20	**7c**	89 (MeOH)	295-296 (decomp)	$C_{14}H_{13}N_3O$ (239)	70.28 (70.13	5.48 5.57	17.56 17.56)	3270, 2225, 1650, 1620	2.41 (s, 3H), 2.44 (s, 3H), 6.33 (s, 1H), 7.06-7.55 (m, 4H) [CF_3COOD]
p-anisidine	5	**7d**	89 (MeOH)	290-291 (decomp)	$C_{14}H_{13}N_3O_2$ (255)	65.87 (65.86	5.13 5.23	16.46 16.72)	3270, 2220, 1630	2.04 (s, 3H), 3.77 (s, 3H), 5.49 (s, 1H), 6.86-7.26 (m, 4H), 9.99 (br, 1H) [DMSO]
m-anisidine	30	**7e**	77 (MeOH)	292-293 (decomp)	$C_{14}H_{13}N_3O_2$ (255)	65.87 (66.02	5.13 5.17	16.46 16.57)	3270, 2225, 1650, 1620	2.30 (s, 3H), 3.85 (s, 3H), 6.08 (s, 1H), 6.70-7.78 (m, 4H) [$CDCl_3$ - CF_3COOD]
p-chloroaniline	40	**7f**	79 (MeOH)	325-326 (decomp)	$C_{13}H_{10}N_3OCl$ (259)	60.12 (60.07	3.88 3.88	16.18 16.27)	3270, 2220, 1650, 1630	2.08 (s, 3H), 5.68 (s, 1H), 7.08-7.60 (m, 4H), 9.19 (br, 1H), 11.38 (br, 1H) [DMSO]

EXPERIMENTAL

All melting points are uncorrected. IR spectra were taken using a Hitachi Model 260-30 spectrophotometer. MS spectra were measured on a JEOL JMS-DX303/JMA-DA5000 instrument. ^{1}H-NMR spectra were recorded on JEOL JNM-GSX400, JNM-EX270, and JNM-PMX60FT

spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard.

4-Hydroxy-6-methyl-2-oxo-3-pyridinecarbonitrile (2) : A suspension of **1** (30 g, 0.2 mol) in 10 % HCl (400 mL) was heated under reflux for 4 h. The precipitate was collected by filtration and washed well with water, and then recrystallized from MeOH to give **2** (26 g, 87 %) **;** mp 300-301℃(decomp) [lit.,[4] mp 295℃(decomp)].

4-Chloro-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (3) : A mixture of **2** (20 g, 133 mmol), $POCl_3$ (41 g, 267 mmol), and PCl_5 (56 g, 267 mmol) in $CHCl_3$ (400 mL) was heated under reflux for 6 h. The reaction mixture was slowly poured into ice-water with vigorous stirring. The resulting mixture was neutralized with a concentrated aqueous ammonia. The precipitate was collected by filtration. The organic layer was separated from the filtrate, and the aqueous layer was extracted with $CHCl_3$ (100 mL). The combined organic layer was washed with water and then dried over anhydrous $CaCl_2$. After the organic layer was concentrated *in vacuo*, the formed precipitate was collected by filtration. The combined precipitate was purified by recrystallization from EtOH to give **3** (16.9 g, 75 %). The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$ to give **4** (0.5 g, 2 %). **3 ;** mp 304-307℃(decomp), IR (KBr): 2225, 1650cm^{-1}, ^{1}H-NMR (DMSO) δ 2.29 (s, 3H), 6.49 (s, 1H), 12.79 (br, 1H), MS (*m/z*): 168 (M^+). *Anal*. Calcd for $C_7H_5N_2OCl$: C, 49.87; H, 2.99; N, 16.62. Found: C, 49.53; H, 2.63; N, 16.66.

Chlorination of 3 with $POCl_3$: A mixture of **3** (1 g, 5.9 mmol) and $POCl_3$ (10 g, 65 mmol) was heated under reflux for 30 min. The reaction mixture was poured into ice-water. The resulting mixture was neutralized with a concentrated aqueous ammonia, and then extracted with $CHCl_3$ (50 mL×3 times). The organic layer was washed with water and then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$, and the crude product was recrystallized from petroleum ether to give **4** (1 g, 90 %) **;** mp 102-103℃[lit.,[9] mp 103-104℃], IR (KBr): 2200, 1560cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 2.62 (s, 3H), 7.31 (s, 1H).

Hydrogenolysis of 3 : A mixture of **3** (1 g, 5.9 mmol) and 5 % Pd-C (50 mg) in MeOH (100 mL) was shaken in a hydrogen atmosphere at rt until the mixture adsorbed 1 mol eq. amount of hydrogen. The reaction mixture was filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$, and the crude product was recrystallized from EtOH to give **5** (0.7 g, 88 %) **;** mp 293-294°C(decomp) [lit.,[11] mp 292-293°C(decomp)], IR (KBr): 2225, 1660cm^{-1}, ^{1}H-NMR (DMSO) δ 2.28 (s, 3H), 6.21 (d, *J* = 7Hz, 1H), 8.01 (d, *J* = 7Hz, 1H), 11.76 (br, 1H), MS (*m/z*): 134 (M^+).

Reactions of 3 with alkylamines and arylamines ; General procedure : A mixture of **3** (0.5 g, 3 mmol) and 2.5 mol eq. amounts of amines in MeOH (50 mL) was heated under reflux for the time shown in Table 2. The formed precipitate was collected by filtration and washed with water and then EtOH. The filtrate was concentrated *in vacuo*. After 10 % HCl (30 mL) was added to the residue, the precipitate was collected by filtration and washed well with water and then EtOH. The combined precipitate was purified by recrystallization from the solvent as shown in Table 2. For the reaction of **3** with methylamine, the procedure was slightly different from the others because the boiling point of methylamine was low and the product (**6c**) easily dissolved in water. Thus, a mixture of **3** (0.5 g, 3 mmol) and 5 mol eq. amounts of methylamine (30 % in MeOH) in MeOH (50 mL) was heated under reflux for 1 h. After cooling in an ice water bath, the formed precipitate was collected by filtration, and washed with a small amount of cold water and then Et_2O. The filtrate was concentrated *in vacuo*. After cold water (2 mL) was added to the residue, the precipitate was collected by filtration and washed with cold water and then Et_2O. The combined precipitate was purified by recrystallization. The physical, spectral, and analytical data of the products (**6** and **7**) are shown in Table 2.

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