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Synthesis of ethyl 5-cyano-6-hydroxy-2-methyl-4-(1-naphthyl)-nicotinate

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Abstract

A novel ethyl 5-cyano-6-hydroxy-2-methyl-4-(1-naphthyl)-nicotinate is successfully synthesized and the structure is determined by XRD, GC–MS analysis, element analysis and NMR spectroscopic in detail. A reaction mechanism for the reaction is proposed.

Pyridine derivatives containing multi-functional groups can be used as drugs such as streptonigrin, streptonigrone (Fig. 1) and lavendamycin which are reported as anticancer drugs, and itavastatin, cerivastatin (Fig. 1) are reported as the HMG-CoA enzyme inhibitors.[1] Moreover, substituted pyridines are reported as leukotriene B_4 antagonists[2] and so on.[3] Furthermore, the pyridine derivative containing 1-naphthyl group has a good activity when used in Suzuki cross-coupling reaction as a ligand, although it is not a chiral molecule.[4]

However, axial chiral pyridine derivatives contained multi-functional groups is not reported. Therefore, it is necessary to investigate the synthesis and application of novel axially chiral pyridine derivatives.

Our aim is to develop a novel axially chiral ligand used for asymmetric catalyzed Suzuki cross-coupling reaction. According to the aim, the title compound was first designed by introducing 1-naphthyl group at the 4-position of pyridine ring. Following the synthesis investigation, the patent synthesis method developed by TAKEDA Chemicals attracted our attention.[2a] We decided to synthesize the designed molecule by the patent method, and the hydroxyl group was also introduced into the molecule for immobilization to a solid phase or a polymer as a catalyst in the future.

In this Letter, we first introduced 1-naphthyl group as a backbone used to design the novel axially chiral naphthyl pyridine derivative.

The synthesis of the above molecules was based on the Hantzsch reaction and then on the aromatization of 1,4-dihydropyridines (DHPs) into target molecules by various kinds of oxidation methods.[5] In this Letter, the novel compounds of 5-cyano-6-hydroxy-2-methyl-4-aryl nicotinate ester (**5**) were synthesized using one-pot method (Scheme 1) and were then characterized by XRD and NMR et al. in detail.

In order to synthesize **5c** according to the reported procedures,[2a] the cheap reagent, benzyl aldehyde, was first used to synthesize compound **5a**[6,7] in the yield of 22%. The structure was determined by NMR and GC–Mass. To our surprise, there is only one methyloxy peak in NMR spectra. The GC–Mass also gives the molecular weight of 268 corresponding to the given formula **5a**, not as 282 with two methyl groups. The success of the synthesis of **5a** encouraged us to synthesize **5b**[6,8] with an yield of 30% (Table 1, entry 2).

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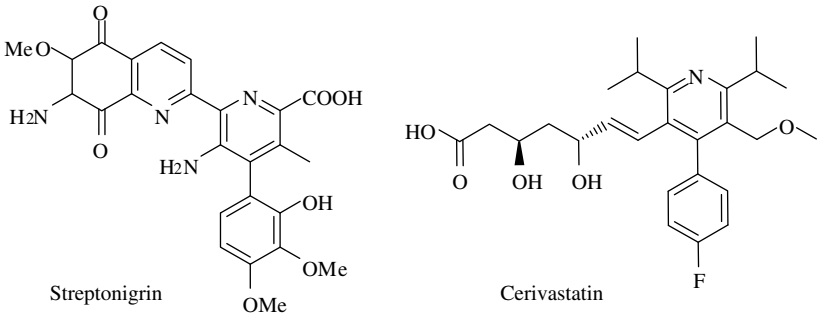


Fig. 1. Pyridine derivatives.

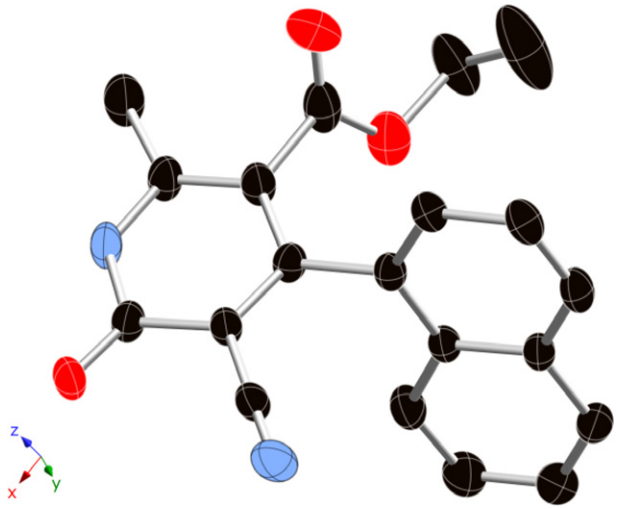


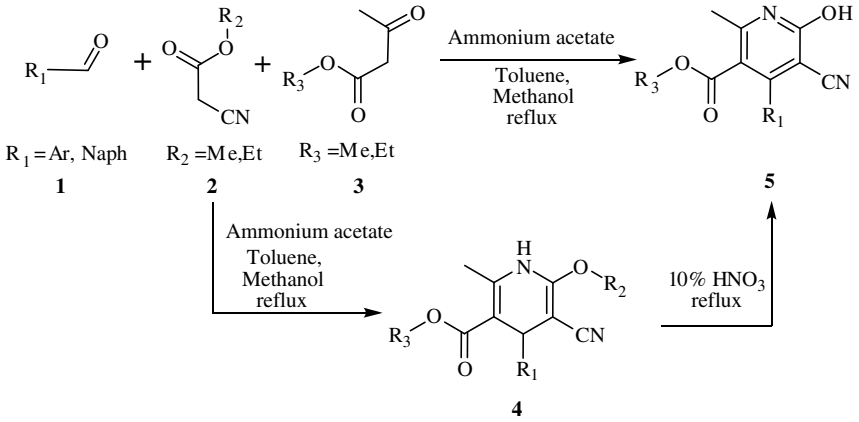
Fig. 2. The crystal structure **5c**. $C_{20}H_{16}N_2O_3$, Mr = 332.35, $Z = 4$, monoclinic, space group $P2(1)/c$, $a = 7.6597(17)$, $b = 17.545$ (3), $c = 13.326$ (3) Å, $V = 1723.0$ (6) Å^3, $\beta = 105.821$ (17), $\rho_{calcd} = 1.281$ g cm^{-3}, μ(MoKα) = 0.712 mm^{-1}, $T = 293(2)$ K, slight yellow block, Crystal size = 0.36 × 0.24 × 0.21 mm^3, 3132 independent measured reflections, F^2 refinement, $R1 = 0.1029$, w$R2 = 0.3679$.

However, the position of the methyloxyl group, whether it is at the 5-position as ester or at the 2-position as ether is not understood. So the title compound **5c**[6,9,10] was synthesized (Table 1, entry 4) to identify the position of methyloxy group. The spectra of **5c** showed that there was only one ethyloxy group in the molecule. At the same time, the reaction (Table 1, entry 3) was carried out with the ethyl cyanoacetate stead of methyl cyanoacetate. There is only **5b** which was obtained with the same yield as entry 2 in Table1. So, the methyl or ethyl group of cyanoacetate was cleaved while the reactions were going on. The title compounds had a hydroxyl group at the 2-position of pyridine ring.

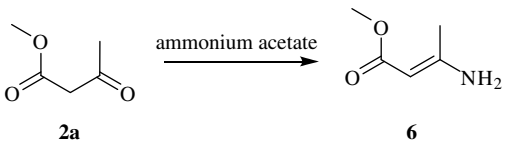
The yield of the reaction is lower when cyanoacetate ester acts as a reactant in the synthesis, but the yield is not worse than that reported. We had investigated the step-by-step reactions for promoting the yield as shown in Schemes 2 and 3, but it was failure, because the reactions between aldehyde and cyanoacetate ester were very quick. In our experiments, intermediate 7 was synthesized in less

Table 1
Synthesis of compounds **5**

Entry	Reactant			Product			Yield (%)
	R_1	R_2	R_3	R_1	R_2		
1	Phenyl	Me	Me	Phenyl	Me	**5a**	22
2	1-Naphthyl	Me	Me	1-Naphthyl	Me	**5b**	30
3	1-Naphthyl	Me	Et	1-Naphthyl	Me	**5b**	30
4	1-Naphthyl	Et	Me	1-Naphthyl	Et	**5c**	37



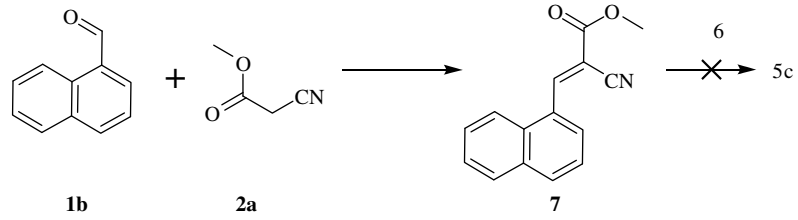
Scheme 1.



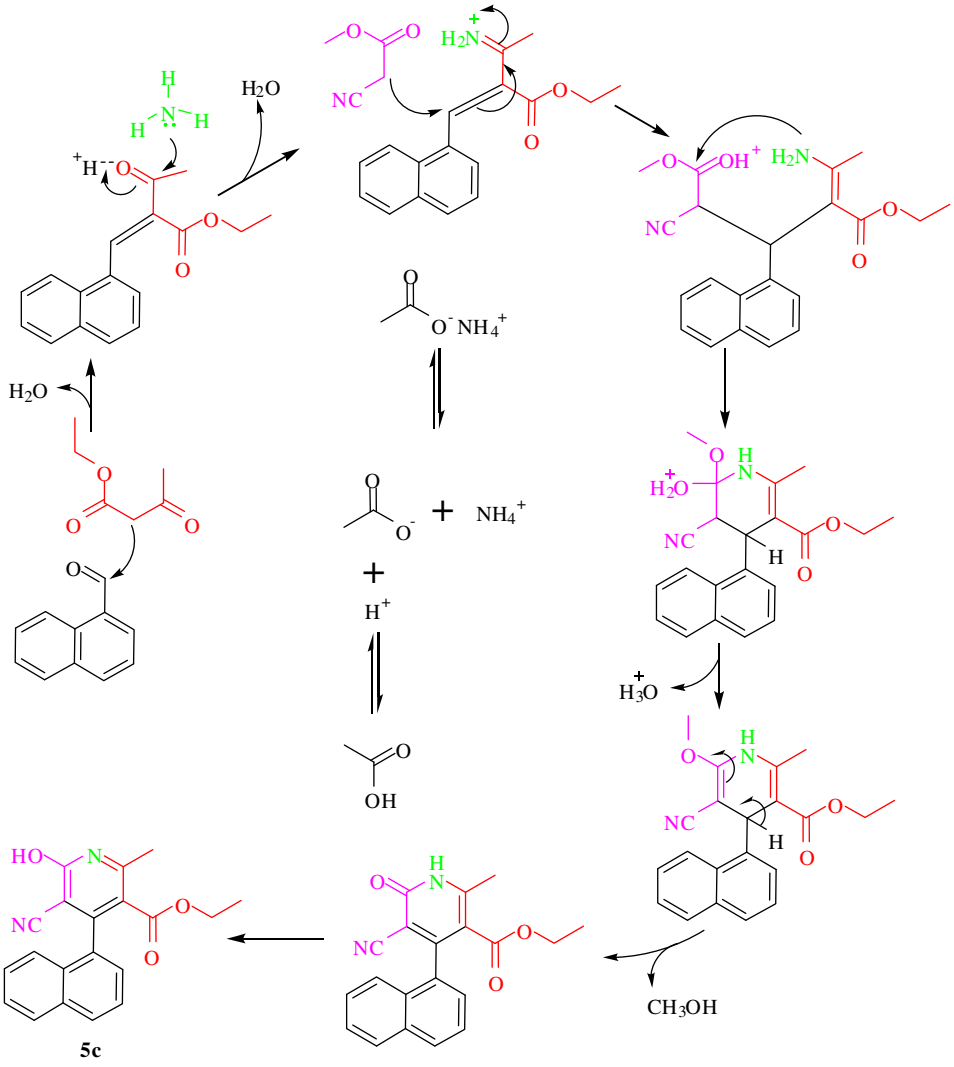
Scheme 2.

than 30 min at an almost 100% yield at room temperature.[13,14] Treatment of **6**[11,12] and **7** was carried out, but no product was obtained even keeping it refluxed for 2 days.

At the same time if aromatic aldehyde was treated first with acetoacetate ester, the product was not pyridine rings; it was the 1,4-dihydropyridines intermediate with good yield which varied from 55% to 96%. The series compounds derived from 1,4-dihydropyridines were synthesized for another kind of substrates to be reported in the future.



Scheme 3.



Scheme 4.

Based on the above experiments, the reaction mechanism was proposed as shown in Scheme 4. Ammonium acetate kept at equilibrium during the reaction as a base to supply ammonium. In the first stage it was concerning the two competitive reactions. One is shown in Scheme 3. The aldehyde reacted with cyanoacetate ester to give 7, but 7 did not react with **6** like the mechanism of Knoevenagel-condensation reaction. This pathway is over. The other is shown in Scheme 4. The aldehyde reacted with acetoacetate ester to give the key intermediate like Knoevenagel condensation, which reacted with ammonium to give the second key intermediate, ester enamine. Then α-hydrogens of cyanoacetate ester were activated enough to permit the deprotonation with a weak base, acetate. Further condensation between cyanoacetate ester and ester enamine was carried out and then went on to give the dihydropyridine derivative by intramolecular cycloaddition. The protons of NH at 4-position and methyl group at 2-position were cleaved, respectively, to give the product by aromatization.

The structure of the product of **5c** was conclusively proved by X-ray Crystallographic Analysis.[10] Figure 2 shows a general view of **5c**.

In conclusion, the synthesis of **5c**, pyridine derivatives containing multiple functional groups with axial chirality, was illustrated. The structure was conclusively determined by X-ray Crystallographic Analysis. The analyst data of **5** were consistent with each other. Because the purpose to synthesize the title compounds was to use it as an asymmetric ligand, further researches on the optical resolution of compounds **5b** and **5c** using enzymes are currently underway.

Acknowledgement

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6. Typical procedure: To a mixture of methanol (30 ml) and toluene (30 ml), ethyl acetoacetate (5.20 g, 40 mmol), 1-naphthaldehyde (6.24 g, 40 mmol), methyl 2-cyanoacetate (3.96 g, 40 mmol) and Ammonium acetate (3.24 g, 42 mmol) were added. The mixture was heated to reflux under stirring for 24 h. The resulting solution were workuped by azeotropic distillation to separate off all toluene, to which water (3 ml) was added. The resulting solvent was kept for refluxing for 24 h and then allowed to cool to room temperature. The light yellow crystals were formed and filtered to give the title compound, and then purified by recrystallization from chloroform-ethyl acetate.
7. Data for 5-cyano-6-hydroxy-2-methyl-4-phenyl-nicotinate (**5a**): Yield 22%; slight yellow solid; crystallized from chloroform-ethyl acetate; MS(EI): *m/z*: 268 [M^+]; MS (FAB+) *m/z*: 269 (MH^+); mp 147–150 °C. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.58 (s, 3H, 2-CH_3), 3.43(s, 3H, –OCH_3), 7.27–7.29 (m, 2H, H_{Ar}), 7.46–7.47 (m, 3H, H_{Ar}), 12.97 (s, 1H, –OH); ^{13}C NMR (400 MHz, DMSO, δ, ppm):18.73, 52.46, 57.74, 85.58, 116.67, 127.62, 129.07, 130.27, 136.38, 147.54, 153.85, 160.14, 166.24; IR (KBr, *v*, cm^{-1}): 3441, 2226, 1733, 1431, 1324, 1288.
8. Data for methyl 5-cyano-6-hydroxy-2-methyl-4-(1-naphthyl)-nicotinate (**5b**): Yield 30%; slight yellow solid; crystallized from chloroform–ethyl acetate; MS (FAB+): *m/z*: 319 [MH^+]; mp 162.9–164.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.58 (s, 3H, OCH_3), 2.98 (s, 3H, CH_3), 7.31–7.34 (dd, $J = 0.91$, 1.36, 7.02, 1H, H_{Ar}), 7.42–7.50 (m, 4H, H_{Ar}), 7.83–7.85 (d, $J = 7.25$, 1H, H_{Ar}), 7.86–7.88 (d, $J = 8.61$, 1H, H_{Ar}), 12.27 (s, 1H, –OH); ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 19.53, 52.20, 76.80, 103.53, 114.15, 115.27, 124.36, 125.16, 125.73, 126.66, 127.25, 128.77, 129.81, 130.27, 133.08, 133.35, 152.94, 160.91, 162.61, 165.16.
9. Data for ethyl 5-cyano-6-hydroxy-2-methyl-4-(1-naphthyl)-nicotinate (**5c**): Yield 37%; slight yellow solid; crystallized from chloroform-ethyl acetate; MS (EI): *m/z*: 332 [M^+]; mp 162.9–164.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 0.32–0.35 (t, 3H, $J = 7.14$, CH_2CH_3), 2.70 (s, 3H, CH_3), 3.49–3.56 (qq, $J = 7.2$, 1H, CH_2), 3.58–3.64 (qq, $J = 7.2$, 1H, CH_2), 7.40–7.42 (dd, $J = 1.50$, 7.2, 1H, H_{Ar}), 7.49–7.57 (m, 4H, H_{Ar}), 7.9–7.92 (dd, $J = 1.50$, 7.0, 1H, H_{Ar}), 7.95–7.97 (d, $J = 8.22$, 1H, H_{Ar}), 12.97 (s, 1H, –OH); ^{13}C NMR (400 MHz, DMSO, δ, ppm): 18.73, 52.46, 57.74, 85.58, 116.67, 127.62, 129.07, 130.27, 136.38, 147.54, 153.85, 160.14, 166.24. IR (KBr, *v*, cm^{-1}): 3434, 2238, 1725, 1398, 1262, 1126, 798, 777; Anal. Calcd for $C_{20}H_{16}N_2O_3$: C 72.28; H 4.85; N 8.43. Found: C 72.42; H 4.90; N 8.36.
10. Crystal data for **5c**: CCDC 677844.
11. Synthesis of methyl 3-aminocrotonate (**6**). According to a modified literature procedure,[5] a solution of methyl acetoacetate (141 mg, 1.21 mmol) and ammonium acetate (550 mg, 7.14 mmol) in methanol (20 ml) was stirred overnight. The solution was concentrated in vacuo and partitioned between water (20 ml) and ethyl acetate (20 ml). The aqueous layer was further extracted with ethyl acetate (3 × 30 ml) and the combined organic layers were washed with brine (15 ml), dried (Na_2SO_4) and evaporated in vacuo to give the title compound **6** as a pale yellow oil.
12. Data for methyl 3-aminocrotonate (**6**): Yield 97; MS(EI): *m/z*: 115 [M^+]; mp 80–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.90 (s, 3H, CH_3), 3.64 (s, 3H, –OCH_3), 4.52 (s, 1H, =CH).
13. Synthesis of methyl 2-cyano-3-(1-naphthyl)-acrylate (**7**). According to a modified literature procedure,[3a] To a stirred mixture of methyl 2-

cyanoacetate (2 mmol) and $Yb(OTf)_3$ (0.06 g, 5 mol %) in ethanol (5 mL), 1-naphthaldehyde (2 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 5 h. The resulting yellow solid was filtered and recrystallized to give the pure title compound **7** as a slight yellow solid.

14. Data for methyl 3-aminocrotonate (**7**): yield >99%. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.99 (s, 3H, OCH_3), 7.57–7.66 (m, 3H, H_{Naph}), 7.92–7.94 (d, $J = 6.81$, 1H, H_{Naph}), 8.03–8.07 (dd, $J = 2.65$, 2.27, 7.96, 2H, H_{Naph}), 8.32–8.34 (d, $J = 7.25$, 1H, H_{Naph}), 9.13 (s, 1H, =CH); MS(EI): m/z: 237 [M^+].