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STEREOCHEMICAL ASPECTS DURING ADDITION REACTION OF 2-CYANO-1,2-DIHYDROISOQUINOLINES WITH BROMINE IN METHANOL WITH AND WITHOUT PYRIDINE

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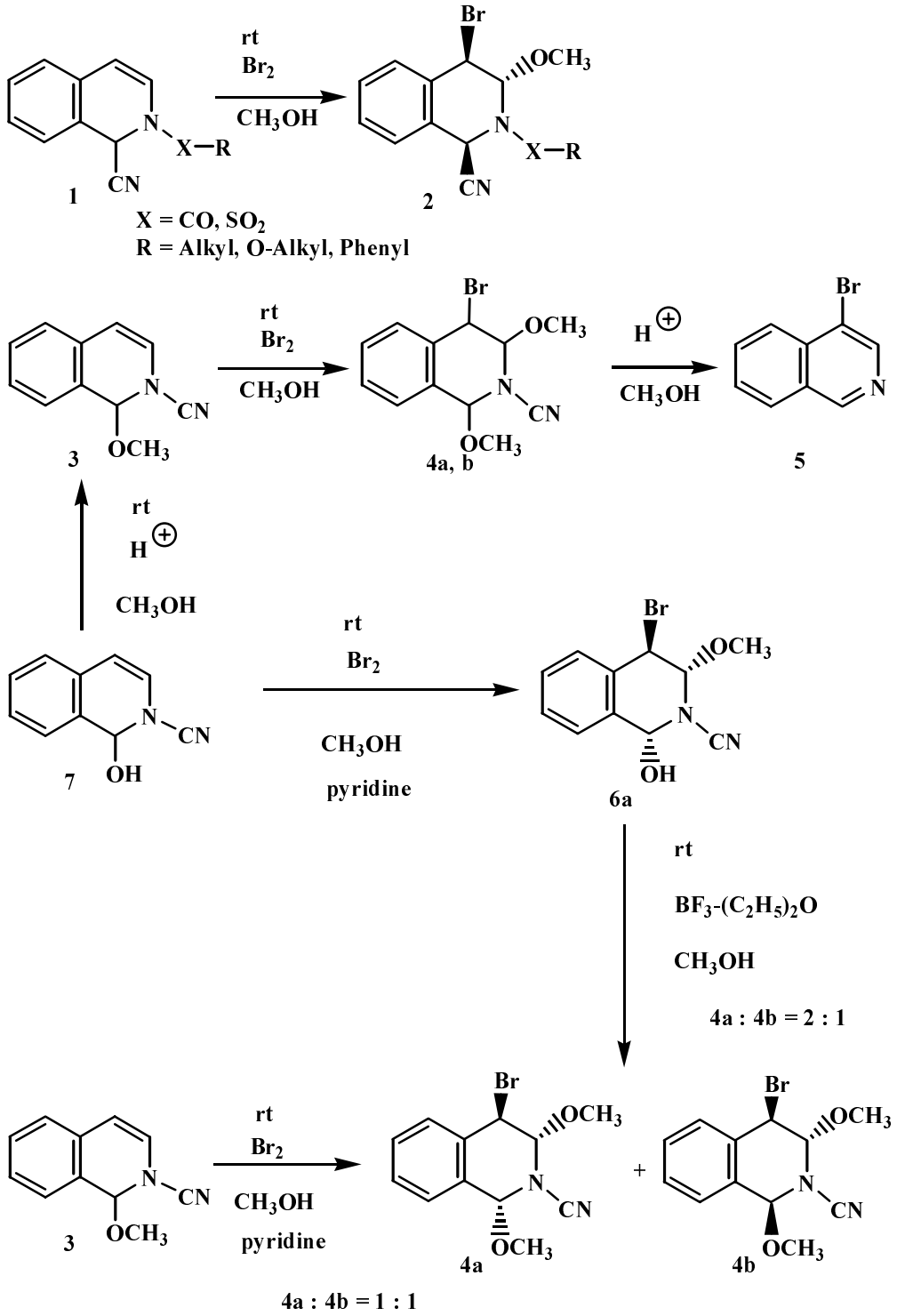
Abstract - 2-Cyano-1-methoxy-1,2-dihydroisoquinoline (**3**) treated with bromine in methanol gave 4-bromo-2-cyano-1,3-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**4**) exhibiting two configurational isomers (**4a** and **4b**). During repeated recrystallization of **4a**, auto-hydrolysis led it to 1-demethylation product (**6**), whereas **4b** was intact giving single crystals. The structures of **4b** and **6a** were determined by X-Ray crystallography. 2-Cyano-1-hydroxy-1,2-dihydroisoquinoline (**7**) treated with bromine in methanol containing pyridine gave **6a** stereoselectively in high yield, whereas from **3** compounds (**4a**) and (**4b**) were afforded in a product ratio of 1 : 1. The mechanisms for the **4a** and **4b** interconvertible reaction and also for the reaction from **7** to **6a** were examined.

Previously,[1] we reported that the reaction of a Reissert compound (**1**) of isoquinoline with bromine in methanol proceeded stereoselectively to form tetrahydroisoquinoline derivative (**2**) exhibiting 1,4-*cis* and 3,4-*trans* relative configurations at high yield (Scheme 1). However, when 2-cyano-1-methoxy-1,2-dihydroisoquinoline (**3**), which has a structure analogous to that of **1,** is used as the starting material, a mixture of two isomers (**4a** and **4b**) is formed. The mixture is converted into a unique product, 4-bromoisoquinoline (**5**) by acid hydrolysis,[2, 3] suggesting that the isomers are configurational ones.

In this study, first, the isomers (**4a)** and (**4b)** were clarified stereochemically. Secondly, because **4a** and **4b** were found in this study to be interconvertible under some acidic conditions, the reaction mechanisms from **3**, derived from 2-cyano-1-hydroxy-1, 2-dihydroiso- quinoline (**7**) by methoxylation,[2] to **4a** and **4b** have been elucidated. On the other hand, **7** treated with bromine under non-acidic conditions containing pyridine gave only one stereospecific isomer of 4-bromo-2-cyano-1-hydroxy-3-methoxy-1,2,3,4-tetrahydroisoquinoline(**6a**), whereas from **3** under the non-acidic conditions **4a** and **4b** were obtained in a ratio of *ca.* 1 : 1. Thus, finally, the stereospecific reaction mechanism from **7** to **6a** has been proposed.



Scheme 1

The mixture of two isomers (**4a**) and (**4b**) was subjected to the high performance liquid chromatography (HPLC)[3] under the conditions shown in Figure 1 for separation. Aliquots were obtained under these conditions. IR, NMR, and MS spectra of each pure substance were measured and the results are shown in Table 1. It is found that the abundance ratio of **4a** to **4b** in the mixture is *ca.* 2 : 1, based on the

integrated intensity of the 1-position hydrogen in the ^{1}H-NMR spectrum and the HPLC peak area. The NOE spectrum of 1,3,4-position hydrogen atoms was measured, but data sufficient for determining the stereochemistry of these compounds were not obtained .

Compounds (**4a**) and (**4b**) were then recrystallized from CH_3OH-CH_2Cl_2 for subsequent X-Ray crystallography. During the repeated recrystallization, however, **4a** changed to a compound (**6a)** through

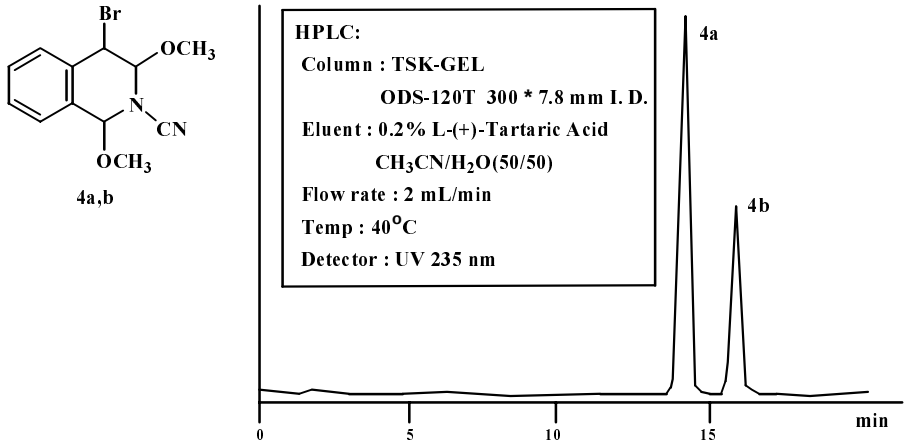


Figure 1. HPLC Analyses of **4a** and **4b**

Table 1. Spectral Properties of **4a, 4b,** and **6a**

Entry	IR ν cm^{-1} (KBr)	MS (FAB^+) m/z (MH^+)	NMR (in $CDCl_3$) 1-H	3-H	4-H	1-OCH_3
4a	2230(CN) 2240(CN)	298	5.73(s)	5.09(d) (J = 1.8 Hz)	5.17(d) (J = 1.8 Hz)	3.70(s)
4b	2230(CN) 2240(CN)	298	5.93(s)	5.12(d) (J = 3.2 Hz)	5.11(d) (J = 3.2 Hz)	3.35(s)
6a	3320(OH) 2220(CN) 2240(CN)	284	5.93(d) (J = 8.4 Hz)	5.10(d) (J = 1.8 Hz)	5.18(d) (J = 1.8 Hz)	

Entry	NMR (in $CDCl_3$) 1-C	3-C	4-C	1-O<u>C</u>H_3	3-O<u>C</u>H_3	CN
4a	85.40	91.11	44.69	56.28	56.66	116.20
4b	84.40	92.31	44.09	52.51	57.72	114.38
6a	78.14	91.34	44.06		57.00	115.55

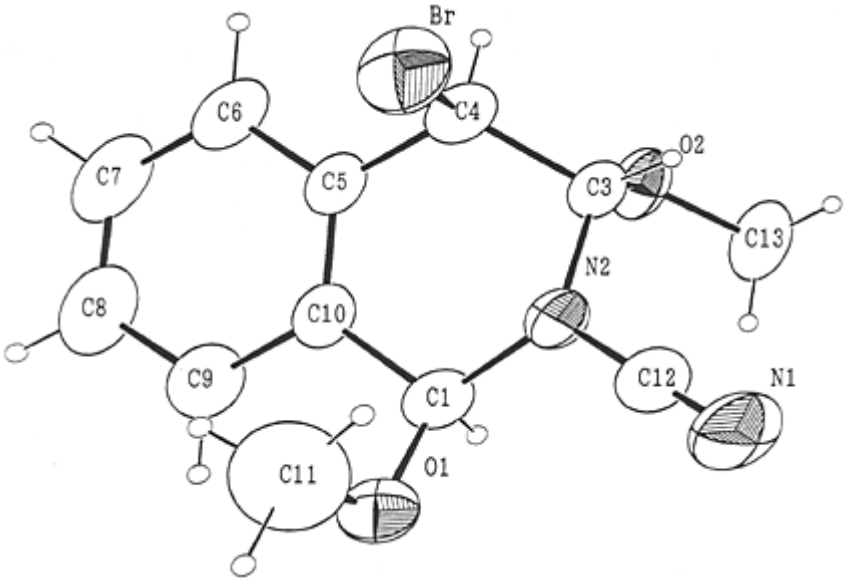


Figure 2. ORTEP Drawing of **4b** with 30 % Probability Ellipsoids for Non-Hydrogen Atoms Octant shaded ellipsoids indicate hetero atoms.

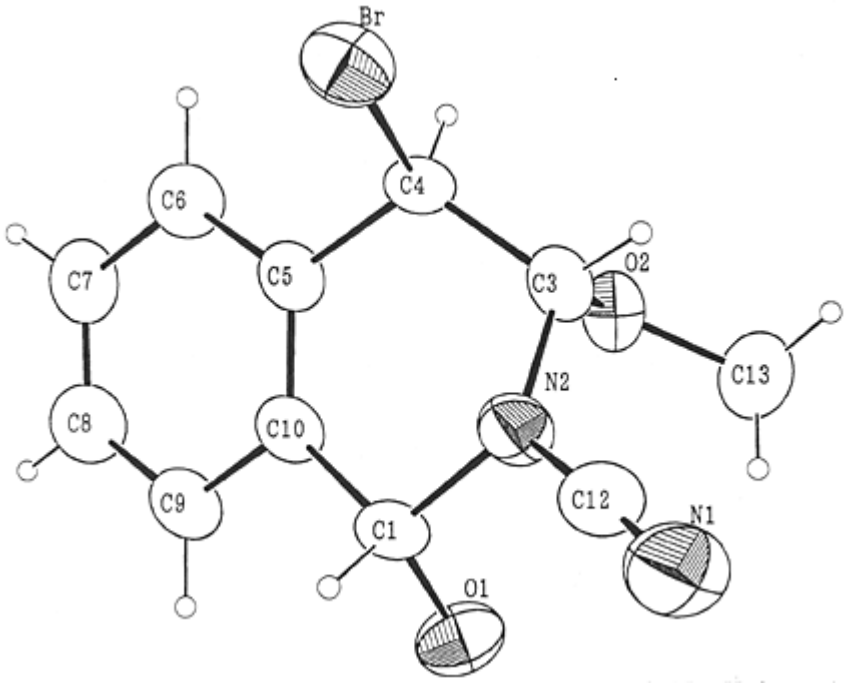
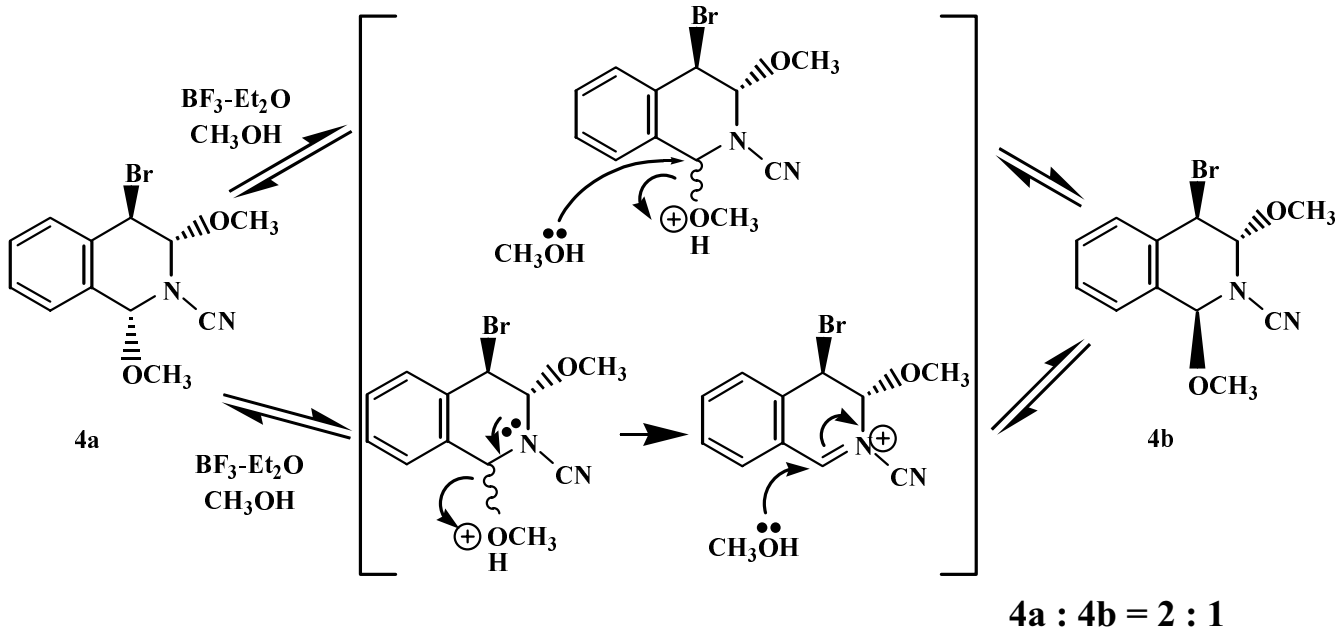


Figure 3. ORTEP Drawing of **6a** with 30 % Probability Ellipsoids for Non-Hydrogen Atoms Octant shaded ellipsoids indicate hetero atoms.



Scheme 2

auto-hydrolysis of the 1-OCH_3 group. Single crystals of **4b** and **6a** were therefore used for X-Ray crystallography. The relative configuration of **4b** was found to be 1,4-*cis* and 3,4-*trans*, and that of **6a** was 1,4-*trans* and 3,4-*trans*, as shown in Figures 2 and 3.

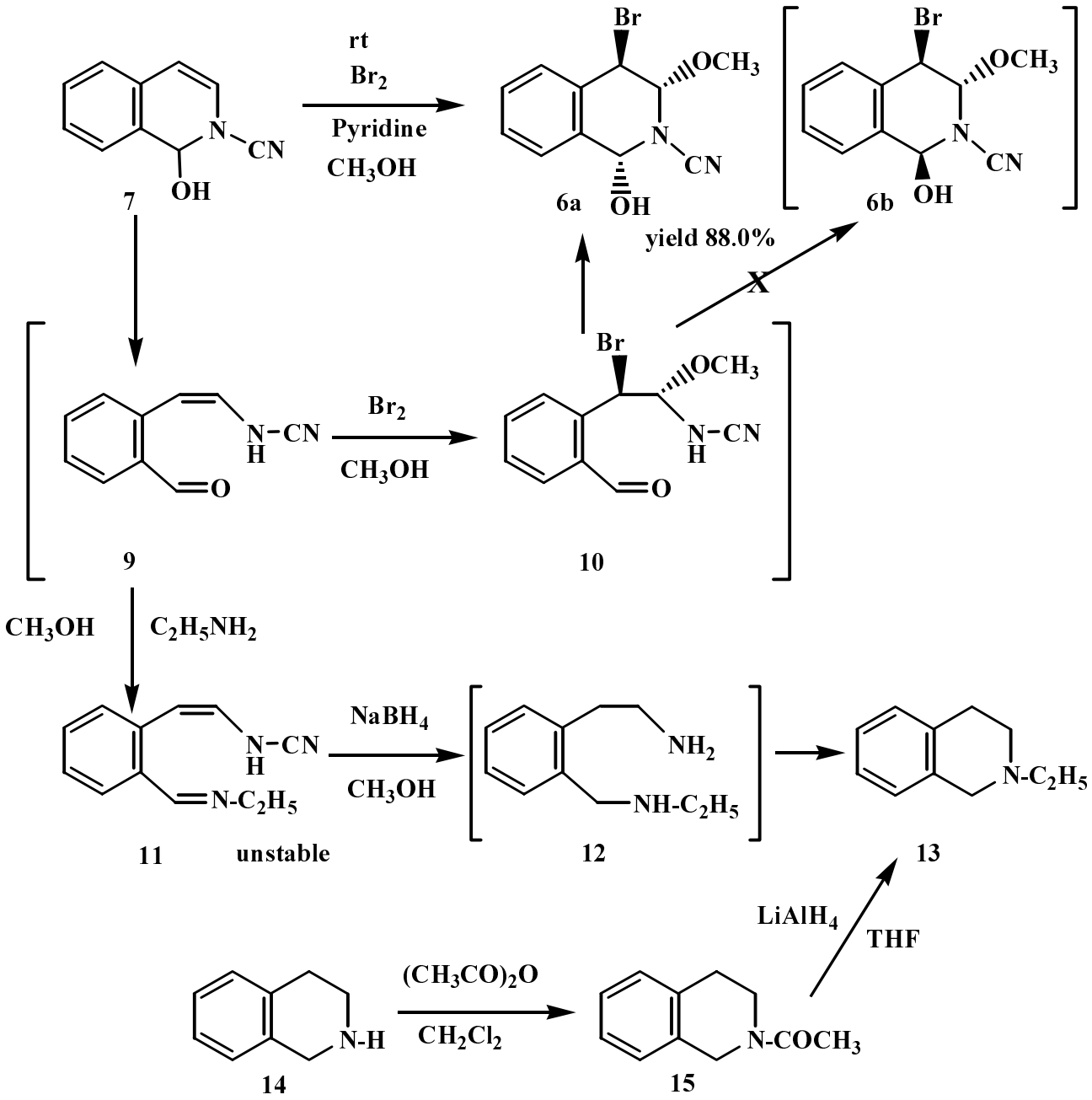
Although conservation of the configuration during auto-hydrolysis from **4a** to **6a** was suggested, methoxylation of the 1-OH group of **6a** to **4a** has been examined by the same methods[2] used for the conversion from **7** to **3**. A mixture of **6a** and BF_3-Et_2O in methanol was left with stirring at room temperature (rt), and a mixture of **4a** and **4b** was obtained in a ratio of 2 : 1 (Scheme 1).

Furthermore, when **4a** or **4b** alone was treated under the same conditions, a mixture in the ratio of 2 : 1 (= **4a** : **4b**) was also obtained. This means that interconversion between **4a** and **4b** occurs under the conditions for the methoxylation of **6a**, *i.e.*, such acidic conditions. A mechanism for the interconversion may involve the substitution of the OCH_3 group at the 1-position by the S_N2 type attack of CH_3OH or the addition of the OCH_3 group to the imminium intermediate (Scheme 2).

In the present bromine addition reactions, the byproduct HBr should function as the acid catalyst in the same way. Thus, the acid-catalyzed Walden inversion at the 1-position can be achieved rapidly to equilibrium in the reaction solution. The formation of **4a** and **4b** in a constant ratio of 2 : 1 should be attributed to a difference in the free energy of formation between **4a** and **4b** in the ground state, *i.e.*, **4a** is stable by about 1.7 kJ/mol calculated from the van't Hoff equation. The ground state free energy difference comprehensively includes electrostatic, steric, conformational, and so on, forces. In this case, we consider that the biggest free energy difference comes from the stereogeometry around the 1-position and that the difference may be derived through *cis*-repulsion between 4-Br and 1-OCH_3 in **4b**.

The evidence is that the chemical shift difference between **4a** and **4b** appears largest at 1-H and 1-OCH_3.

In order to remove the interconversion reactions, pyridine as a base was added with the purpose of reducing HBr acidity during the reaction from **3** to **4a** and **4b**. The reaction resulted in a mixture ratio of 1 : 1



Scheme 3

(Scheme 1). This result suggests that the bromination of **3** occurs statistically in the initial product ratio of 1 : 1 (= **4a** : **4b**), because pyridine terminates the acid-catalyzed reactions. The apparent stereoselectivity (**4a** : **4b** = 2 : 1) therefore comes only from the thermodynamics of the interconversion reaction mentioned above.

It is predicted that if **7** instead of **3** is used for the reaction using pyridine, the 1-OH group will not be methoxylated because of non-acidic conditions[2] and the ordinary bromine addition product should be formed as a stereoisomer mixture (**6a** : **6b** = 1 : 1). To our surprise, however, only **6a** was formed at a

yield of 88.0 % and no 1,4-*cis* and 3,4-*trans* compound (**6b**) was formed (Scheme 3).

Because **7** has a 1-OH group (not methoxylated), **7** undergoes ring-opening (**9)** and the *trans* addition of bromine gives **10**, as shown in Scheme 3. During ring-closure (*i.e.*, an attack by the lone pair of the N atom in the –NH-CN group on the carbonyl carbon atom in the benzoyl group) steric repulsion among 4-Br, 1-OH, 2-CN, and 3-OCH_3 groups may occur in the case of **6b**, and thus **6a** is solely formed. It is suggested that the stereoselectivity in this case comes from the transition (or excited) state free energy difference in the kinetic process from **10** towards **6a**, *i.e.*, the repulsion among 4-Br, 1-OH, 2-CN, and 3-OCH_3 may be affected more effectively in the transition state than in the ground state.

To confirm the existence of ring-opened compound (**9)** in this reaction mechanism, the mixture of **7** and ethylamine as a primary amine in methanol solution containing pyridine was left. As the result, generation of Schiff base (**11)** was confirmed by NMR and MS spectra. However, compound (**11)** is unstable and decomposes readily during column chromatography. Compound (**11)** was then reduced with $NaBH_4$ in methanol and 2-ethyl-1,2,3,4-tetrahydroisoquinoline (**13**) was obtained through the compound (**12)** shown in Scheme 3. Compound (**13)** was confirmed separately based on the IR and NMR spectra of compound (**15)** obtained by acetylation of 1,2,3,4-tetrahydroisoquinoline (**14**) and the reduction of **15** with $LiAlH_4$.

As described previously,[1] from compounds bearing a CO or SO_2 group on the N atom, a 1,4-*cis* isomer is selectively obtained through the addition reaction of 1,2-dihydroisoquinoline derivatives with bromine. On the other hand, it was found that in the case of compounds having a CN group on the N atom, the stereoselectivity depends on the substituent on the 1-carbon atom. The reason why the stereoselectivity depends on the difference in substituents on the N atom and the 1-C atom will be a subject of future examination, and the starting materials with various substituents should be tested.

EXPERIMENTAL

General Details

Melting points were measured using a Yanagimoto micromelting point apparatus and are reported without correction. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL JNM A-400 (400 MHz) and JEOL JNM A-600 (600 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ). MS were taken with JEOL HX-110 and Hitachi M-80B-GC-MS spectrometers. The aluminum oxide used for the column chromatography was Merck Alminiumoxid 90 active, neutral (70 - 230 mesh). The silica gel used for the chromatography was Merck Silica Gel 60 (70 - 230 mesh). HPLC analyses were performed with a JASCO 880-PU, JASCO 860-CO, JASCO 880-30, and JASCO 880-50, equipped with JASCO 870-UV detector operating at a wavelength of 235 nm. The column was a TSK-GEL ODS-120T (300 x 7.8 mm I. D. ; Tokyo, Japan), and the temperature of the column oven was set at 40 $^\circ$ C. The mobile phase was aqueous acetonitrile (50 v/v %) with 0.2 % L-(+)-tartaric acid which was pumped at a flow rate of 2.0 mL min^{-1}.

4-Bromo-2-cyano-1,3-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4a and 4b) and 4-bromo-2-cyano-1-hydroxy-3-methoxy-1,2,3,4-tetrahydroisoquinoline (6a)

Compounds (**4a**) and (**4b**) were isolated from the reaction product[3] by HPLC. The ratio of **4a** and **4b** before the separation of the mixture was 2 : 1 which was estimated by the NMR spectrum. They were recrystallized from methanol. The repeated recrystallization of **4a** from methanol afforded **6a**. The spectral properties of **4a, 4b,** and **6a** are shown in Table 1.

Reactions of 4a, 4b, and 6a with $BF_3 \cdot Et_2O$

To a solution of **4a, 4b**, or **6a** (0.1 mmol) in methanol (20 mL) was added $BF_3 \cdot Et_2O$ (1 mL), and the mixture was stirred at rt for 24 h. The reaction mixture was poured into water and extracted with CH_2Cl_2, and the CH_2Cl_2 solution was washed with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. ^{1}H-NMR spectrum and HPLC data for the residue showed that the mixture ratio of **4a** and **4b** was 2 : 1.

Bromination reactions of 2-cyano-1-hydroxy (or methoxy)-1,2-dihydroisoquinolines (3, 7)

To a stirred solution of **3** or **7** (0.1 mol) in CH_2Cl_2 (250 mL) and pyridine (10 mL) CH_3OH (200 mL) and bromine (17.6 g, 0.11 mol) were added slowly at 0 - 20 ° C, and the entire mixture was kept at rt for 0.5 h. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 20 % $NaHSO_3$ and next 5 % $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The crystalline residue was recrystallized from benzene-hexane (1 : 1) to give a mixture of **4a** and **4b** from **3**, and **6a** from **7**. ^{1}H-NMR spectrum and HPLC data of the residue showed that the mixture ratio of **4a** and **4b** was 1 : 1. The yields of **4a**, **4b**, and **6a** were 45.0 %, 45.0 %, and 88.0 %, respectively.

2-Ethyl-1,2,3,4-tetrahydroisoquinoline (13) : From 7

To a stirred solution of **7** (1.72 g, 0.01 mol) in CH_2Cl_2 (20 mL) and pyridine (10 mL) ethylamine (0.90 g, 0.02 mol) was added slowly at 10 ° C, and the mixture was kept at rt for 1 day. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The oily residue was Schiff-base (**11**) of which the purity was over 90 % from gas chromatography estimation. Compound (**11**) was unstable and could be used for the next reaction. The pure compound could not be obtained. Yield : 2.03 g, 91.5%.

To a stirred solution of crude **11** (2.21 g, 0.01 mol) in CH_3OH (200 mL) $NaBH_4$ (1.14 g, 0.03 mol) was added slowly at 0 ° C, and the mixture was kept at rt for 4 h. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The residue was 2-ethyl-1,2,3,4-tetrahydroisoquinoline (**13**). The total yield of **13** from **7** was 54.0 % (0.87 g) and was identified as the product prepared from **14** by NMR and IR spectra.

Table 2. Summary of Crystal Data and Intensity Collection Parameters for **4b** and **6a**

	4b	**6a**
Formula	$C_{12}H_{13}N_2O_2Br$	$C_{11}H_{11}N_2O_2Br$
M	297.15	283.12
Crystal size/mm	0.18 x 0.30 x 0.42	0.18 x 0.30 x 0.36
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/c$
T /K	293	293
a / Å	8.000(1)	8.467(1)
b / Å	8.798(2)	17.492(6)
c / Å	9.561(1)	8.574(1)
α /°	80.25(2)	90
β /°	75.75(1)	117.51(44)
γ /°	74.69(1)	90
V / Å^3	625.1(2)	1126.1(57)
Z	2	4
F(000)	284	600
Dx /g cm^{-3}	1.504	1.753
μ /cm^{-1}	32.42	36.03
Diffractometer	Enraf-Nonius CAD4	
Radiation	Graphite monochromated Mo-K α	
2 θ range /°	4 — 52	4 — 52
Scan technique	ω - 2 θ	ω - 2 θ
Scan range(ω) /°	0.69 + 0.83 tan θ	0.55 + 0.71 tan θ
No. of measured data	2602	2456
No. of unique obsd data [$F_o > 3.0\ \sigma(F_o)$]	2029	1613
R [a]	0.059	0.073
Rw [b]	0.063	0.087
No. of variables	154	145

a) $R = \Sigma\,||Fo| - |Fc||\,/\,\Sigma\,|Fo|$; b) $Rw = [\,\Sigma\, w(\,|Fo| - |Fc|\,)^2 / \Sigma\, wFo^2]^{1/2}$ where w = 1.

From 1,2,3,4-tetrahydroisoquinoline (14)

To a stirred solution of **14** (13.3 g, 0.1 mol) in CH_2Cl_2 (200 mL) acetic anhydride (20.4 g, 0.2 mol) was added slowly at 10 ° C, and the mixture was kept at rt for 1 h. The reaction mixture was poured into ice water, extracted with CH_2Cl_2 and the CH_2Cl_2 solution was washed with 5 % $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The crystalline residue was recrystallized from benzene-hexane (1 : 1) to give 2-acetyl-1,2,3,4-tetrahydroisoquinoline (**15**). The yield was 88.2 % (15.46 g) and the product was identified as the product prepared from isoquinoline[4] by NMR and IR spectra.

To a stirred solution of **15** (0.175 g, 0.01 mol) in anhydrous THF (200 mL) $LiAlH_4$ (1.14 g, 0.03 mol) was added slowly at 0 ° C, and the mixture was kept at rt for 4 h. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The residue was 2-ethyl-1,2,3,4-tetrahydroisoquinoline (**13**). The yield was 1.21 g, 75.0%. Compound (**13)** was identified as the product prepared from **7** and isoquinoline[5] by NMR and IR spectra.

X-Ray crystallography of 4b and 6a

The crystal data and information are given in Table 2, and the ORTEP drawings are shown in Figures 2 and 3. Both structures were solved and refined routinely. [6,7]

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