Polycyclic *N*-Heterocyclic Compounds. **48**. Syntheses of Furo[2,3-*h*]-[1,6]naphthyridine and Imidazo(or Pyrimido)[2,1-*f*]-[1,6]naphthyridines with Rearrangement

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The formation of a novel ring system, furo[2,3-*h*][1,6]naphthyridine *via* the Smiles rearrangement and intramolecular cyclization is described. Cyclization of 5-(ω-hydroxyalkylamino)-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridines provided novel spiro compound with rearrangement.

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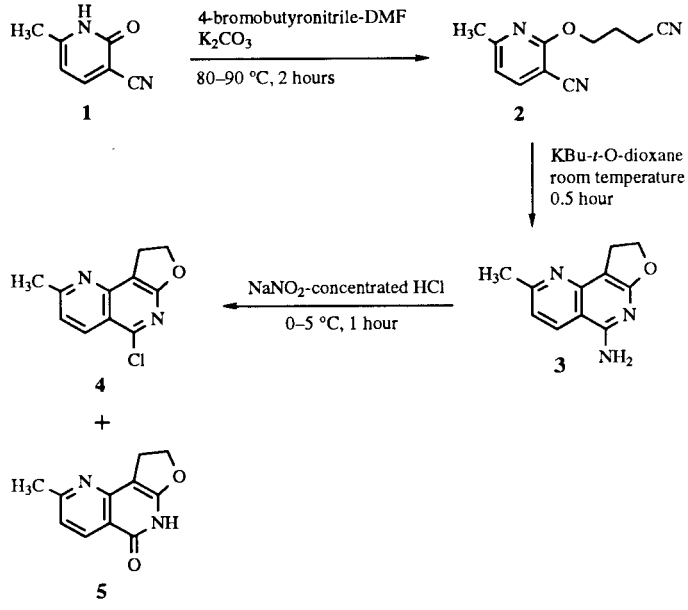
We have reported a new route for the synthesis of 5-amino-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine from the intramolecular nucleophilic rearrangement of 2-(3-cyanopropylthio)pyridine-3-carbonitrile with potassium *tert*-butoxide, which was analogous to the Smiles rearrangement [1,2] followed by intramolecular cyclization [3]. From this preliminary finding 5-amino-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]naphthyridine was prepared from another dinitrile substrate, namely, 2-(3-cyanopropylthio)-6-methylpyridine-3-carbonitrile [4]. As an application of our studies on novel naphthyridine derivatives, we report at this time the syntheses of 1,2-dihydrofuro[2,3-*h*]-[1,6]naphthyridine, 2,3,5,6-tetrahydroimidazo[2,1-*f*]-[1,6]naphthyridine, and 3,4,6,7-tetrahydro-2*H*-pyrimido[2,1-*f*][1,6]naphthyridine skeletons. Among these ring systems, two compounds have a spiro cyclopropane ring.

Result and Discussion.

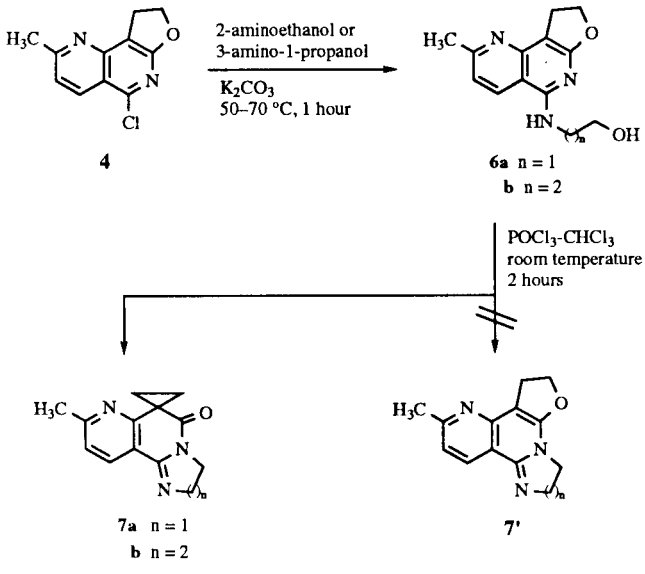
The required 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*]-[1,6]naphthyridine (**3**) was prepared by the procedure shown in Scheme 1. The commercially available 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**1**) was employed as a starting material. Reaction of compound **1** with 4-bromobutyronitrile in *N*,*N*-dimethylformamide (DMF) provided 2-(3-cyanopropoxy)-6-methylpyridine-3-carbonitrile (**2**). Treatment of **2** with potassium *tert*-butoxide in dioxane at room temperature gave **3** in 83% yield. The structure of **3** was assigned by spectral and elemental analyses as follows: The ir spectrum of the product gave absorptions at 3420 and 3140 cm^{-1} that are characteristic of amino group. The ^1H nmr spectrum (200 MHz) of **3** showed two methylene proton signals as triplets at δ 3.24 ppm and δ 4.58 ppm, pyridine ring proton signals at δ 7.01 ppm and δ 8.36 ppm, and amino proton signal at δ 7.09 ppm, respectively. The mechanism of this polycyclic heterocyclic ring formation seemed to be similar to that proposed previously [3], that is, this compound was obtained through a Smiles type intramolecular rearrangement followed by nucleophilic cyclization.

Scheme 1



To explore the feasibility of molecular modification of **3** to prepare furonaphthyridines, some reactions were performed as shown in Schemes 1 and 2. Compound **3** upon diazotization with sodium nitrite in concentrated hydrochloric acid afforded 5-chloro-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine (**4**) and 8-methyl-5-oxo-1,2,4,5-tetrahydrofuro[2,3-*h*][1,6]naphthyridine (**5**) in a yield of 34% and 21%, respectively. Consecutive treatment of **4** with 2-aminoethanol and 3-amino-1-propanol gave **6a**,**b** in 69% and 77% yields, respectively. The attempted cyclization of **6** with phosphorus oxychloride did not give the desired product **7'** rather gave the spiro compounds **7**. We propose a reaction pathway for formation of this ring shown in Scheme 3. Initially, intermediate **8** which was formed from compound **6** with phosphorus oxychloride cyclized to hydrochloride **9**. After that, compound **9** was transformed to **11** *via* **10** followed by rearrangement to produce compound **7** as the hydrochloride. This compound was basified with sodium hydrogen carbonate to afford **7**

Scheme 2



4

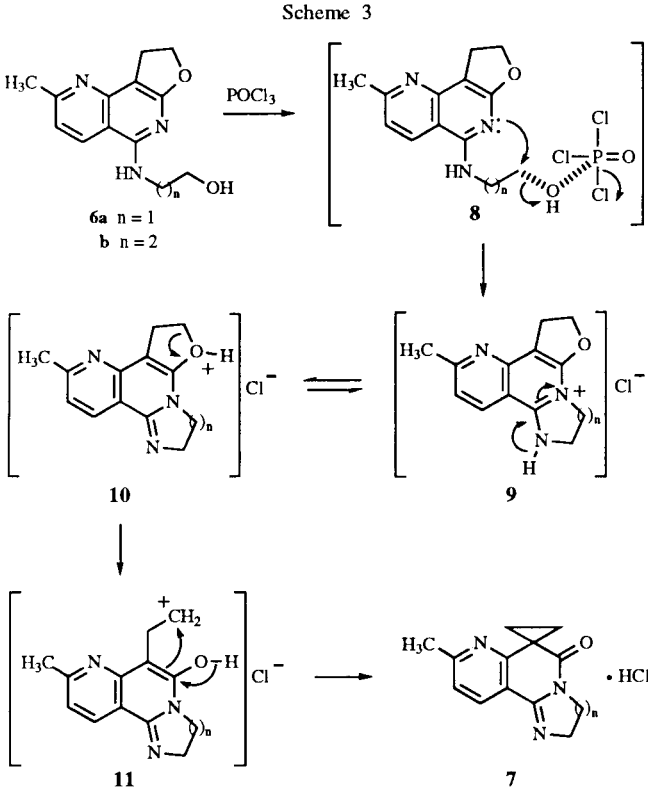
6a n = 1
b n = 2

7a n = 1
b n = 2

7'

as free base. In the ir spectra, both absorptions of each amide carbonyl group of **7a,b** were observed at 1670 cm^{-1}. In the ^1H nmr spectrum (200 MHz) of **7a** in deuteriochloroform, four proton multiplet centered at δ 1.89 ppm was observed as cyclopropane ring protons of the AA'BB' type with a pattern similar to that observed for the cyclopropane ring protons of spiro[cyclopropane-1,4'(1'*H*)-isoquinoline]-1',3'(2'*H*)-dione [5,6]. On the other hand, the signal of the corresponding protons of **7b** was observed at δ 1.89 ppm as a singlet. This appearance seemed to be an accidental phenomenon.

Scheme 3



6a n = 1
b n = 2

8

10

9

11

7

In conclusion, we have successfully synthesized 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine (**3**) by a route involving an intramolecular nucleophilic rearrangement analogous to the Smiles rearrangement, that was followed by intramolecular nucleophilic cyclization. Furthermore, rearrangement of **6** underwent formation of imidazo(or pyrimido)spiro compounds **7**. Thus, we have demonstrated the feasibility of this route to synthesize naphthyridines and its spiro derivatives utilizing a simple technique.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The EI-mass , FAB-mass, and high-resolution mass spectra were measured on a VG 70 mass spectrometer. In the case of FAB-mass, glycerol or *m*-nitrobenzyl alcohol was used as a matrix agent. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer and frequencies are expressed in cm^{-1}. The ^1H nmr spectra were recorded on a Varian VXR-200 instrument in the solvent indicated with tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ) and J values in Hz, and the signals are designated as follow; s, singlet; d, doublet; t, triplet; quin; quintet, m, multiplet; br, broad.

2-(3-Cyanopropoxy)-6-methylpyridine-3-carbonitrile (**2**).

To a suspension of 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (25 g, 0.19 mole) in DMF (280 ml) were gradually added 4-bromobutyronitrile (55 g, 0.37 mole) and potassium carbonate (51 g, 0.37 mole) under gentle stirring. The resulting mixture was heated at 80–90° for 2 hours. Ice-water (2800 g) was poured into the mixture and allowed to stand for 12 hours after which the product precipitated out as a crystalline solid, and collected *in vacuo*. The solid was recrystallized from a mixture of cyclohexane-benzene to afford **2** as colorless plates (28.5 g, 76%), mp 85–87°; ir (potassium bromide): ν max 2220 (CN); ms: FAB m/z 202 (MH^+); ^1H nmr (deuteriochloroform): 2.19 (quin, J = 7, 2H, OCH_2CH_2), 2.50 (s, 3H, CH_3), 2.61 (t, J = 7, 2H, CH_2CN), 4.54 (t, J = 7, 2H, OCH_2), 6.85 (d, J = 7.7, 1H, H5), 7.76 (d, J = 7.7, 1H, H4).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.78; H, 5.62; N, 20.78.

5-Amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine (**3**).

To a stirred suspension of **2** (3.0 g, 14.9 mmoles) in dioxane (60 ml) was gradually added potassium *tert*-butoxide (2.5 g, 22.3 mmoles). The reaction mixture was stirred at room temperature for 0.5 hour. Ice-water (600 g) was added and the mixture was kept standing for 6 hours during which time the compound precipitated out as a crystalline solid. It was collected *in vacuo*. The solid was recrystallized from ethanol to give **3** as pale

brown prisms (2.50 g, 83%), mp 279–280°; ir (potassium bromide): ν max 3420 and 3140 (NH); ms: EI m/z 201 (M^+, 100%), 200 (M^+ - H, 60%); ^1H nmr (DMSO-d_6): 2.53 (s, 3H, CH_3), 3.24 (t, J = 8.7, 2H, CH_2CH_2O), 4.58 (t, J = 8.7, 2H, OCH_2), 7.01 (d, J = 8.5, 1H, H7), 7.09 (br s, exchangeable with deuterium oxide, 2H, NH_2), 8.36 (d, J = 8.5, 1H, H6).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.51; H, 5.48; N, 20.70.

5-Chloro-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine (**4**) and 8-Methyl-5-oxo-1,2,4,5-tetrahydrofuro[2,3-*h*][1,6]naphthyridine (**5**).

To a stirred solution of **3** (3.76 g, 18.7 mmoles) in concentrated hydrochloric acid (250 ml) was added sodium chloride (25 g). The mixture was kept at 0– -5°. The aqueous sodium nitrite (6.45 g, 93.5 mmoles) solution was gradually added over a period of 1 hour. The resulting mixture was neutralized with saturated aqueous sodium hydrogen carbonate solution and allowed to stand for 6 hours. After that, the precipitated crystalline solid was collected by suction. The filtrate was extracted with benzene (100 ml), the organic layer was washed with brine, and dried over anhydrous magnesium sulfate. The organic solvent was evaporated, and the residue was combined with the above solid obtained by suction. The combined solid was subjected to column chromatography on silica gel with a mixture of chloroform-acetone as the eluting solvent to afford two major products: the less polar product was eluted with chloroform-acetone (9:1, v/v) and recrystallized from benzene to give **4** (1.4 g, 34%) as pale yellow feathers, mp 128–130°. On the other hand, the more polar product was eluted with chloroform-acetone (1:1, v/v) and recrystallized from ethanol to afford **5** (0.8 g, 21%) as colorless feathers, mp 256° dec.

Compound **4** had ms: FAB m/z 221 (MH^+), 223 ($MH^+ + 2$); ^1H nmr (deuteriochloroform): 2.74 (s, 3H, CH_3), 3.61 (t, J = 9, 2H, OCH_2CH_2), 4.84 (t, J = 9, 2H, OCH_2), 7.20 (d, J = 8.7, 1H, H7), 8.35 (d, J = 8.7, 1H, H6)

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 60.00; H, 4.23; N, 12.73.

Compound **5**: ir (potassium bromide): ν max 3460 (NH), 1660 (CO); ms: FAB m/z 203 (MH^+); ^1H nmr (deuteriochloroform): 2.64 (s, 3H, CH_3), 3.39 (t, J = 9.0, 2H, OCH_2CH_2), 4.84 (t, J = 9.0, 2H, OCH_2), 7.02 (d, J = 8.3, 1H, H7), 8.44 (d, J = 8.3, 1H, H6), 11.50 (br s, exchangeable with deuterium oxide, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.85. Found: C, 65.18; H, 5.08; N, 13.92.

5-(2-Hydroxyethylamino)-8-methyl-1,2-dihydrofuro[2,3-*h*]-[1,6]naphthyridine (**6a**).

A mixture of 4 (220 mg, 1.0 mmole), potassium carbonate (207 mg, 1.5 mmoles), and 2-aminoethanol (1 ml) was heated at 60–70° for 1 hour. Ice-water (10 g) was added to the reaction mixture, which was neutralized with acetic acid. After precipitation of the crystalline solid in the mixture, the solid was collected by suction. The filtrate was extracted with chloroform (20 ml), the organic layer was washed with brine, and dried over anhydrous magnesium sulfate. The organic solvent was evaporated, and the residue was combined with the above solid obtained by suction. The solid was recrystallized from a mixture of cyclohexane-ethanol to afford **6a** as yellowish orange plates (170 mg, 69%), mp 178–181°; ir (potassium bromide): ν max 3340 (OH) and 3150 (NH); ms: FAB m/z 246 (MH^+); ^1H nmr (deuteriochloroform): 2.65 (s, 3H, CH_3), 3.45 (t, J = 8.9, 2H, H1), 3.77 [two proton triplet (J = 5) was superimposed with a broad one proton signal, which changed to a two proton triplet (J = 5) after addition of deuterium oxide, 3H, NCH_2 and OH or NH], 3.91 (t, J = 5, 2H, NCH_2CH_2O), 4.73 (t, J = 8.9, 2H, H2), 5.80 (br s, exchangeable with deuterium oxide, 1H, NH or OH), 6.95 (d, J = 8.5, 1H, H7), 7.87 (d, J = 8.5, 1H, H6).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.43; H, 6.19; N, 17.40.

5-(3-Hydroxypropylamino)-8-methyl-1,2-dihydrofuro[2,3-*h*]-[1,6]naphthyridine (**6b**).

A stirred mixture of 4 (220 mg, 1.0 mmole), potassium carbonate (207 mg, 1.5 mmoles), and 3-amino-1-propanol (1 ml) was heated at 50–70° for 1 hour. The reaction mixture was quenched with ice-water (10 g) and neutralized with acetic acid. The aqueous suspension was extracted with chloroform (50 ml), the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was recrystallized from a mixture of cyclohexane-ethanol to give **6b** as yellow plates (200 mg, 77%), mp 159–161°; ir (potassium bromide): ν max 3390 (OH and NH); ms: FAB m/z 260 (MH^+); ^1H nmr (deuteriochloroform): 1.86 (quin, J = 6, 2H, $CH_2CH_2CH_2$), 2.66 (s, 3H, CH_3), 3.45 (t, J = 8.9, 2H, H1), 3.67-3.82 (m, changed to four proton multiplet after addition of deuterium oxide, 5H, $NCH_2CH_2CH_2O$ and OH or NH), 4.72 (t, J = 8.9, 2H, H2), 5.82 (br s, exchangeable with deuterium oxide, 1H, NH or OH), 6.95 (d, J = 8.5, 1H, H7), 7.84 (d, J = 8.5, 1H, H6).

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.63; H, 6.75; N, 16.15.

2',3'-Dihydro-8'-methylspiro[cyclopropane-1,6'(5'*H*)-imidazo-[2,1-*f*][1,6]naphthyridin]-5'-one (**7a**).

To a stirred suspension of **6a** (200 mg, 0.82 mmole) in chloroform (3 ml) was added phosphorus oxychloride (0.15 ml, 1.63 mmoles) portionwise. The mixture was stirred at room temperature for 2 hours and evaporated in reduced pressure to give an oily residue, which was quenched with water (20 ml). The resulting mixture was basified with saturated aqueous sodium hydrogen carbonate solution, and then extracted with dichloromethane (30 ml). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography on octadecyl-functionalised silica gel with chloroform as an eluting solvent to afford a solid which was recrystallized from benzene to give **7a** as dark pink prisms (50 mg, 27%), mp 138–140°; ir (potassium bromide): ν max 1670 (CO); ms: FAB m/z 228 (MH^+); ^1H nmr (deuteriochloroform): 1.89 (m, 4H, H-cyclopropane ring), 2.53 (s, 3H, CH_3), 4.00 and 4.14 (each m, each 2H, H2 and H3), 7.08 (d, J = 8, 1H, H9), 8.20 (d, J = 8, 1H, H10).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.53; H, 5.74; N, 18.39.

3',4'-Dihydro-9'-methylspiro[cyclopropane-1,7'(6'*H*)-[2*H*]-pyrimido[2,1-*f*][1,6]naphthyridin]-6'-one (**7b**).

To a stirred suspension of **6b** (200 mg, 0.77 mmole) in chloroform (1 ml) was gradually added phosphorus oxychloride (0.14 ml, 1.54 mmoles). The resulting suspension was stirred at room temperature for 2 hours. Excess solvent and reagent were removed *in vacuo* to obtain an oily residue which was quenched with water (20 ml). The mixture was basified with saturated aqueous sodium hydrogen carbonate solution. The resulting sus-

pension was extracted with dichloromethane (40 ml), the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was subjected to column chromatography on octadecyl-functionalised silica gel with chloroform as an eluting solvent to afford a solid which was recrystallized from benzene to give **7b** as dark pink prisms (80 mg, 43%), mp 105–107°; ir (potassium bromide): ν max 1670 (CO); ms: FAB m/z 242 (MH^+); ^1H nmr (deuteriochloroform): 1.89 (s, 4H, H-cyclopropane ring), 1.96 (quin, J = 5.7, 2H, H3), 2.50 (s, 3H, CH_3), 3.70 and 3.90 (each t, J = 5.5, each 2H, H2 and H4), 7.03 (d, J = 8.2, 1H, H10), 8.29 (d, J = 8.2, 1H, H11).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.40; H, 6.18; N, 17.31.

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REFERENCES AND NOTES

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