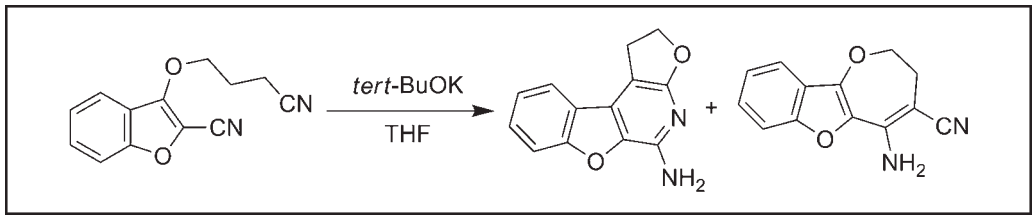
Polycyclic *N*-Heterocyclic Compounds, Part 69: Synthesis of 5-Amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo [2,3-*b*]pyridines and Their Transformations to Related Compounds

Kensuke Okuda,[a]* Jun-ichi Takano,[b] Takashi Hirota,[b] and Kenji Sasaki[b]

[a]Laboratory of Medicinal and Pharmaceutical Chemistry, Gifu Pharmaceutical University, Gifu 501-1196, Japan
[b]Laboratory of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Okayama University, Kita-ku, Okayama 700-8530, Japan
*E-mail: okuda@gifu-pu.ac.jp

Received August 2, 2010
DOI 10.1002/jhet.772
Published online 21 November 2011 in Wiley Online Library (wileyonlinelibrary.com).



Reaction of 3-(3-cyanopropoxy)[1]benzofuran-2-carbonitriles with potassium *tert*-butoxide gave 5-amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridines and 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitriles as new ring systems. Reactions of the 5-chloro derivative, obtained from 5-amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine, produced a dihydrofuran ring-opened compound and 5-substituted compounds.

J. Heterocyclic Chem., **49**, 281 (2012).

INTRODUCTION

We are engaged in on-going studies on the syntheses and biological evaluation of heterocyclic compounds containing new ring systems [1]. During the course of this work, we have developed a new synthetic method for the preparation of aromatic fused furo[2,3-*b*]pyridines (**2**) by reaction of 2-(3-cyanopropoxy)aryl-1-carbonitriles (**1**) with bases (Scheme 1) [2–5]. The reaction mechanism of this transformation involves Truce-Smiles rearrangement followed by intramolecular cyclization to give **2** [2]. The Truce-Smiles rearrangement belongs to a class of useful rearrangement reactions that provide access to complex structures from easy-accessible precursors through formation of new C—C bonds [6–10]. Further interest prompted us to extend this unique strategy using 3-(3-cyanopropoxy)benzofuran-2-carbonitriles (**3a–c**) as starting materials. These are more challenging substrates because the electron rich benzofuran is less reactive than the aromatic systems that we used previously for the Truce-Smiles rearrangement. As far as we know, there are no reports of the relatively electron-rich benzofuran heterocycles undergoing aromatic nucleophilic substitution reactions such as that required for the Truce-Smiles rearrangement.

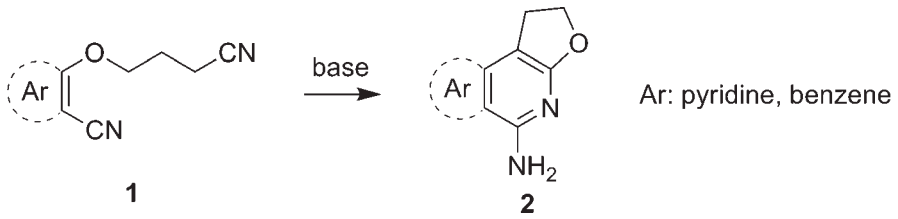
RESULTS AND DISCUSSION

As shown in Scheme 2, **4a–c** [11–13] were allowed to react with 4-chlorobutyronitrile in the presence of potassium carbonate and potassium iodide to give **3a–c**. Compounds **3a–c** showed two cyano bands in their IR spectra, one of which corresponded to conjugated absorption and the other to unconjugated absorption.

Reaction of **3a** with potassium *tert*-butoxide in dry THF gave 5-amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo [2,3-*b*]pyridine (**5a**, 17%), the product of a Truce-Smiles rearrangement and 5-amino-2,3-dihydro[1]benzofuro [3,2-*b*]oxepin-4-carbonitrile (**6a**, 39%) formed by Thorpe-Ziegler reaction. These products as new ring systems were separable by silica gel column chromatography. Although these two compounds have the same molecular formula, the characteristic amino absorption in the IR spectrum of **5a** and the amino and cyano bands of **6a** clearly supported each isomer identification. This is the first time we have observed a product of the Thorpe-Ziegler reaction in our studies. Formation of **6a** can be ascribed to the fact that the less activated benzofuran moiety disfavors the *ipso* attack that is essential for the Truce-Smiles rearrangement. Similarly, **3b** gave **5b** (36%) and **6b** (29%), **3c** gave **5c** (12%) and **6c** (23%), respectively. In those cases, higher temperature was required to effect a smooth reaction.

We previously reported that the reaction of ethyl 2-(3-cyanopropoxy)cyclohexene-1-carboxylate (**7**) with potassium *tert*-butoxide gave 1,2,6,7,8,9-hexahydrofuro[2,3-*c*]isoquinolin-5(4*H*)-one (**8**) by this rearrangement-cyclization reaction (Scheme 3) [14]. To explore the scope of this reaction, we prepared compound **9**, which, similar to compound **7**, has a cyano group as

Scheme 1. Substrate (**1**) with base and rearranged product (**2**).

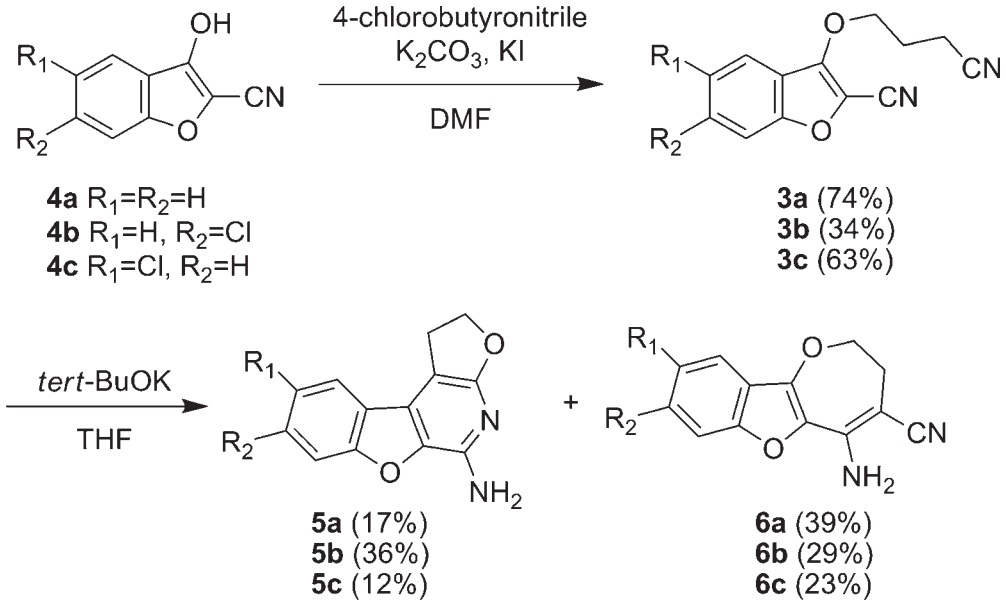


well as the adjacent alkyl chain linked ester moiety. This corresponds to replacement of the 3-(3-cyanopropoxy) group of **3a** with the 3-(3-ethoxycarbonylpropoxy) group. Reaction of **4a** with ethyl 4-bromobutyrate in the presence of potassium carbonate and potassium iodide in DMF gave **9**. This was allowed to react with potassium *tert*-butoxide to produce the Truce-Smiles rearrangement product 3-(2-oxo-2,3,4,5-tetrahydrofuran-3-yl) [1]benzofuran-2-carbonitrile, **10** (37% yield) and a lower yield of the Thorpe-Ziegler reaction product, ethyl 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carboxylate, **11** (10% yield) (Scheme 4). In the IR spectrum of **10**, cyano and lactone carbonyl bands are present at 2230 and at 1755 cm^{-1}. In compound **11,** there is no cyano group band but an amino group absorption is present at 3420, 3310 cm^{-1} along with an ester carbonyl band at 1645 cm^{-1}. A plausible mechanism for the formation of **10** is shown in Scheme 5. An initial loss of a proton from the α-carbon of the ester carbonyl group of **9** is followed by intramolecular nucleophilic addition of the carbanion at the *ipso* position. This is followed by ring opening of the resulting spiroether to give an intermediate oxyanion. Intramolecular attack of the oxyanion on the ester moiety produces lactone **10**.

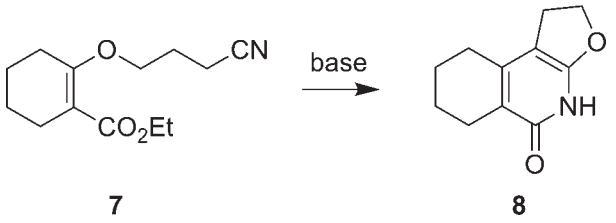
As described above, the 5-amino derivative **5a** is a novel heterocyclic ring and provides a new scaffold for the preparation of additional drug-like analogues whose pharmaceutical activity we wished to evaluate. We thus converted **5a** to the 5-chloro derivative (**12**) for subsequent substitution with nucleophiles. Diazotization of **5a** with sodium nitrite and conc. hydrochloric acid gave the expected **12** in 46% yield. Disappearance of amino band and appearance of chlorine atom were confirmed in the IR and ms spectral data of **12**. Reaction of **12** with 2-aminoethanol in 1,4-dioxane under reflux afforded the 5-(2-hydroxyethylamino) derivative (**13a**) in 9% yield (Scheme 6). A similar reaction of **12** with 2-sulfanylethanol afforded 5-(2-hydroxyethylsulfanyl) derivative (**13b**) in 34% along with a 7% yield of the dihydrofuran ring-cleaved product (**14**) [15]. Finally, morpholine was allowed to react with compound **12** and the substitution product **15** was obtained in 46% yield.

In summary, we have developed a method for the synthesis of 5-amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-

Scheme 2. Synthesis of **5** and **6**.



Scheme 3. Substrate (**7**) with base and rearranged product (**8**).



7 **8**

b]pyridines (**5**) based on the Truce-Smiles rearrangement and 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitriles (**6**) based on the Thorpe-Ziegler reaction. The 5-amino group of **5a** was transformed to the chloro derivative (**12**), which was allowed to react with nucleophiles to give 5-substituted derivatives. We are currently exploring the biological properties of the products with the goal of developing new pharmaceutical agents.

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 electron impact (EI)-mass, fast atom bombardment (FAB)-mass (*m*-nitrobenzyl alcohol was used as the matrix), and electron spray ionization (ESI)-mass spectra were obtained on a VG 70 mass spectrometer or Micromass AutoSpec-OA-Tof. The IR spectra were recorded on a Japan Spectroscopic diffraction grating A-102 or FT/IR-200 spectrophotometer and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument or a Hitachi R-1500 instrument with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and *J* values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). TLC was carried out on Kieselgel 60F254 (Merck) or silica gel 70FM (Wako).

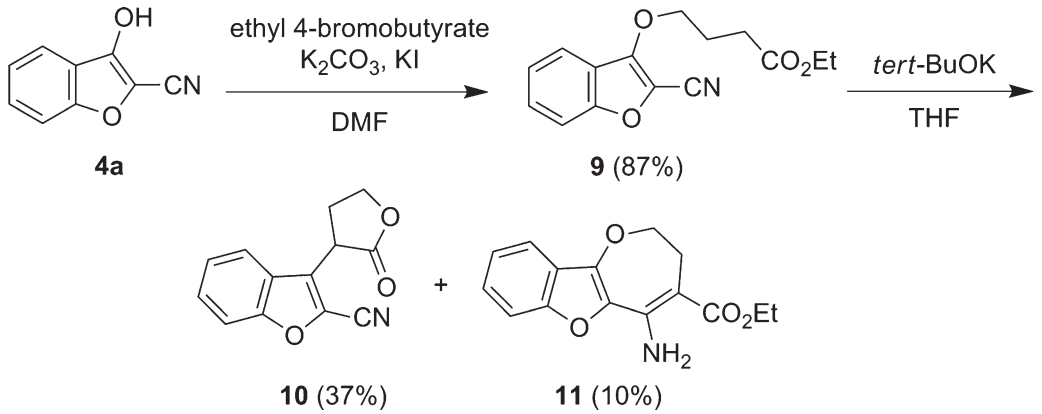
3-Hydroxy[1]benzofuran-2-carbonitrile (4a). Compound **4a** was synthesized according to the ref. 11. M.p. 138–142°C (ref. 11; 145–147°C); IR (potassium bromide): 3220 (OH), 2225 (CN) cm^{-1}; (chloroform): 3080 (OH), 2217 (CN), 1740 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 5.23 (s, 0.3H, deuterium oxide exchangeable, CHCN), 7.90–8.27 (br, 0.7H, deuterium oxide exchangeable, OH), 7.25–7.82 (m, 4H, H4, 5, 6, and 7), as tautomeric mixtures, (DMSO-d_6): δ 7.20–7.85 (m, 4H, H4, 5, 6, and 7), 12.01 (br, 1H, deuterium oxide exchangeable, OH), as an enol form [16]; EI-ms *m*/*z*: 159 (M^+). Anal. Calcd. for $C_9H_5NO_2$: C, 67.92; H, 3.17; N, 8.80. Found: C, 67.82; H, 3.39; N, 8.71.

6-Chloro-3-hydroxy[1]benzofuran-2-carbonitrile (4b). Compound **4b** was synthesized according to the ref. 12. M.p. 182°C (dec.) (ref. 12; m.p. 205°C); IR (potassium bromide): 3170 (OH), 2230 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.44 (dd, 1H, J = 9.0, 2.0 Hz, H5), 7.83 (d, 1H, J = 2.0 Hz, H7), 7.88 (d, 1H, J = 9.0 Hz, H4), 12.30 (br s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m*/*z*: 194 (MH^+), 196 (MH^+ + 2). Anal. Calcd. for $C_9H_4ClNO_2$: C, 55.84; H, 2.08; N, 7.24. Found: C, 55.75; H, 2.44; N, 7.16.

5-Chloro-3-hydroxy[1]benzofuran-2-carbonitrile (4c). Compound **4c** was synthesized according to the ref. 13. M.p. 180–185°C (ref. 13; 211°C); IR (potassium bromide) cm^{-1}: 3220 (OH), 2230 (CN); ^{1}H-NMR (DMSO-d_6): δ 7.60 (dd, 1H, J = 9.0, 2.0 Hz, H6), 7.66 (d, 1H, J = 9.0 Hz, H7), 7.91 (d, 1H, J = 2.0 Hz, H4), 12.26 (br s, 1H, deuterium oxide exchangeable, OH); EI-ms *m*/*z*: 193 (M^+), 195 (M^+ + 2). Anal. Calcd. for $C_9H_4ClNO_2$: C, 55.84; H, 2.08; N, 7.24. Found: C 56.01; H, 2.40; N, 7.31.

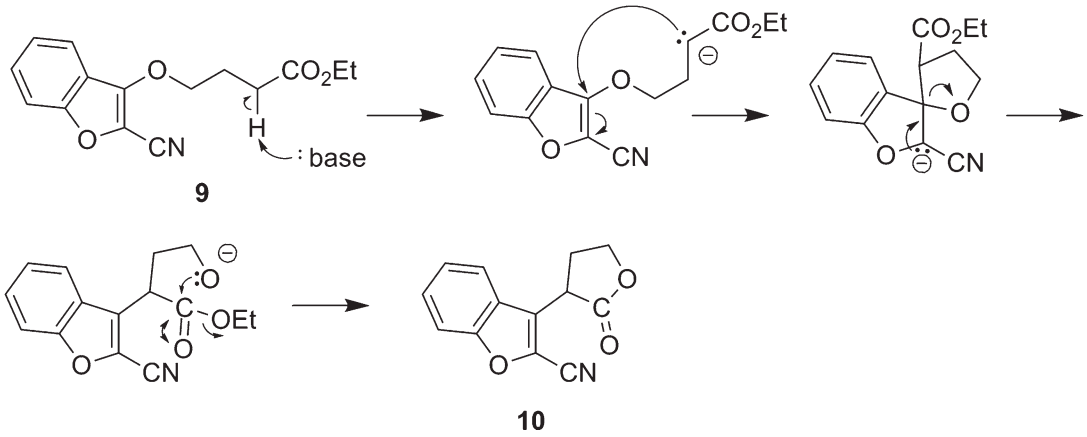
3-(3-Cyanopropoxy)[1]benzofuran-2-carbonitrile (3a). To a mixture of **4a** (10.0 g, 62.8 mmol), potassium carbonate (13.0 g, 94.1 mmol), and potassium iodide (160 mg, 0.964 mmol) in dry DMF (25 mL) was added dropwise 4-chlorobutyronitrile (9.00 mL, 101 mmol) in dry DMF (15 mL) during 3 h under stirring. The reaction was continued for an additional 3 h at 80°C. The solid was filtered off and the mother liquid was evaporated *in vacuo*. Water (100 mL) was poured into the residue, and the mixture was extracted with hot ethyl acetate (50 mL × 10). The combined organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized from cyclohexane to give **3a** (10.5 g, 74%) as pale brown needles, m.p. 99–100°C; IR (potassium bromide): 2240, 2210 (CN) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.17–2.88 (m, 4H, CH_2CH_2CN), 4.61 (t, 2H, J = 6.0 Hz, OCH_2), 7.22–7.77

Scheme 4. Synthesis of **10** and **11**.



4a **9** (87%) **10** (37%) **11** (10%)

Scheme 5. Mechanistic proposal for formation of **10**.

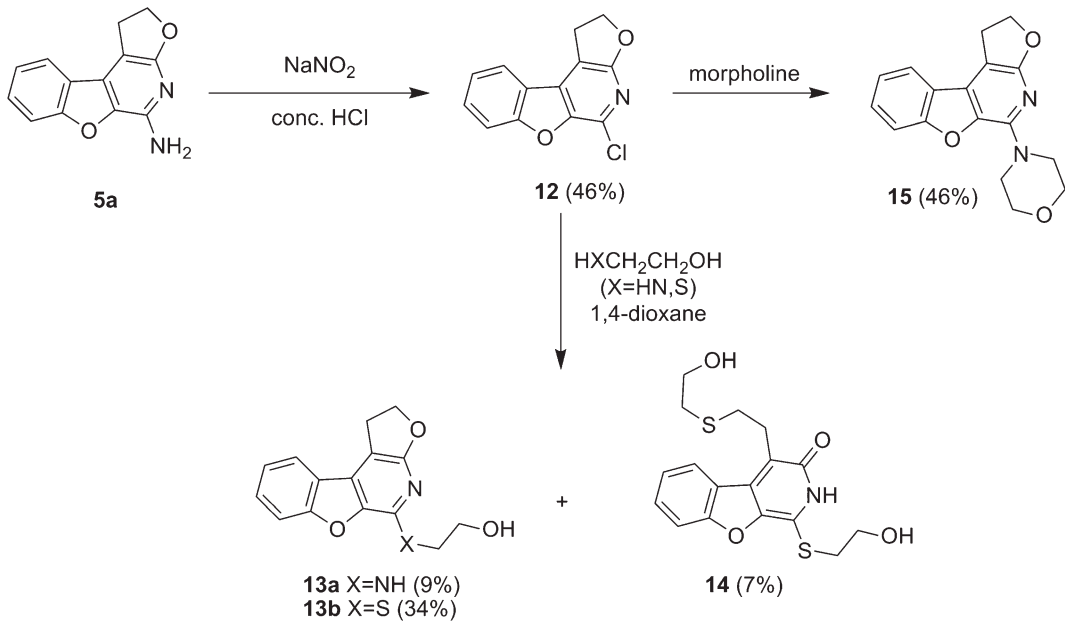


(m, 4H, H4, 5, 6, and 7); FAB-ms *m/z*: 227 (MH^+). Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.18; H, 4.60; N, 12.22.

6-Chloro-3-(3-cyanopropoxy)[1]benzofuran-2-carbonitrile (3b). To a mixture of **4b** (1.00 g, 5.17 mmol), potassium carbonate (1.10 g, 7.96 mmol), and potassium iodide (30.0 mg, 0.181 mmol) in dry DMF (10 mL) was added dropwise 4-chlorobutyronitrile (0.720 mL, 8.05 mmol) in dry DMF (8.0 mL) during 4 h under stirring and the reaction was continued at 80°C for 6 h. The solid was removed by filtration and the mother liquid was evaporated *in vacuo*. Water (100 mL) was poured into the residue, and the mixture was extracted with ethyl acetate (50 mL × 4). The combined organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, evaporated *in vacuo*, and the residue was chromatographed on silica gel. The eluate of cyclohexane-ethyl acetate (5:1) was evaporated *in vacuo* and recrystallized from cyclohexane-benzene to give **3b** (470 mg, 34%) as colorless needles, m.p. 89°C; IR (potassium bromide): 2240, 2210 (CN) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.05–2.80 (m, 4H, CH_2CH_2CN), 4.61 (t, 2H, J = 6.0 Hz, OCH_2), 7.23–7.70 (m, 3H, H4, 5, and 7); FAB-ms *m/z*: 261 (MH^+), 263 ($MH^+ + 2$). Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 60.07; H, 3.66; N, 10.69.

5-Chloro-3-(3-cyanopropoxy)[1]benzofuran-2-carbonitrile (3c). To a mixture of **4c** (200 mg, 1.03 mmol), potassium carbonate (200 mg, 1.45 mmol), and potassium iodide (5.0 mg, 0.0301 mmol) in dry DMF (2.0 mL) was added dropwise 4-chlorobutyronitrile (0.120 mL, 1.34 mmol) in dry DMF (6.0 mL) during 3 h under stirring. The reaction was then continued for an additional 5 h at 80°C. The solid was filtered off and the mother liquid was evaporated *in vacuo*. Water (150 mL) was poured into the residue, and the solution was extracted with ethyl acetate (100 mL × 3). The combined organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized from benzene to give **3c**

Scheme 6. Synthesis of **13**, **14**, and **15.**



(170 mg, 63%) as colorless prisms, m.p. 113–114°C; IR (potassium bromide): 2235, 2222 (CN) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.32–2.43 (m, 2H, $CH_2CH_2CH_2$), 2.56 (t, 2H, J = 6.0 Hz, CH_2CN), 4.61 (t, 2H, J = 6.0 Hz, OCH_2), 7.02–7.83 (m, 3H, H4, 6, and 7); EI-ms *m*/*z*: 260 (M^+), 262 ($M^+ + 2$). Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.97; H, 3.61; N, 10.73.

5-Amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (5a) and 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitrile (6a). To a solution of **3a** (4.00 g, 17.7 mmol) in dry THF (250 mL) was added potassium *tert*-butoxide (2.40 g, 21.4 mmol), and the reaction was stirred at room temperature for 0.5 h. After removal of solvent by evaporation *in vacuo*, ice water (100 mL) was poured into the residue, and the mixture was extracted with ethyl acetate (50 mL × 6). The combined organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, evaporated *in vacuo* and the residue was chromatographed on silica gel. The eluate of benzene was evaporated *in vacuo,* and the yellow solid residue was recrystallized from benzene to give **6a** (1.55 g, 39%) as a pale yellow powder. The further eluate of benzene-ethyl acetate (4:1) was evaporated *in vacuo*, and the brown solid residue was recrystallized from benzene to give **5a** (690 mg, 17%) as pale brown needles. **5a**: m.p. 260°C; IR (potassium bromide): 3480, 3290, 3150 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.42 (t, 2H, J = 8.0 Hz, H1), 4.64 (t, 2H, J = 8.0 Hz, H2), 6.18–6.39 (br, 2H, deuterium oxide exchangeable, NH_2), 7.25–8.01 (m, 4H, H7, 8, 9, and 10); FAB-ms *m*/*z*: 227 (MH^+). Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.14; H, 4.55; N, 12.46. **6a**: m.p. 205°C; IR (potassium bromide): 3450, 3300, 3200 (NH), 2170 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.71 (t, 2H, J = 4.1 Hz, H3), 4.41 (t, 2H, J = 4.1 Hz, H2), 6.21 (br s, 2H, deuterium oxide exchangeable, NH_2), 7.26–7.72 (m, 4H, H7, 8, 9, and 10); FAB-ms *m*/*z*: 227 (MH^+). Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.03; H, 4.61; N, 12.23.

5-Amino-8-chloro-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (5b) and 5-amino-8-chloro-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitrile (6b). To a preheated solution of **3b** (1.00 g, 3.84 mmol) in dry THF (25 mL) at 60°C was added potassium *tert*-butoxide (470 mg, 4.19 mmol) in one portion and the reaction was then refluxed for 5 min. After removal of solvent *in vacuo*, ice water (100 mL) was poured into the residue. The precipitated solid was collected by filtration and was chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (4:1) was collected and evaporated *in vacuo*. The yellow solid residue was recrystallized from benzene to give **6b** (290 mg, 29%) as pale yellow needles. The eluate of *n*-hexane-ethyl acetate (1:1) was evaporated *in vacuo*. The brown solid residue was recrystallized from ethyl acetate to give **5b** (360 mg, 36%) as brown granules. **5b**: m.p. 262–264°C; IR (potassium bromide) cm^{-1}: 3260, 3140 (NH); ^{1}H-NMR (DMSO-d_6): δ 3.41 (t, 2H, J = 8.0 Hz, H1), 4.64 (t, 2H, J = 8.0 Hz, H2), 6.32 (br, 2H, deuterium oxide exchangeable, NH_2), 7.44 (dd, 1H, J = 8.0, 2.0 Hz, H9), 7.80 (d, 1H, J = 2.0 Hz, H7), 7.96 (d, 1H, J = 8.0 Hz, H10); EI-ms *m*/*z*: 260 (M^+), 262 ($M^+ + 2$). Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.98; H, 3.69; N, 10.79. **6b**: m.p. 116–118°C; IR (potassium bromide): 3470, 3350, 3210 (NH), 2180 (CN) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.79 (t, 2H, J = 4.0 Hz, H3), 4.40 (t, 2H, J = 4.0 Hz, H2), 4.93 (br s, 2H, deuterium oxide exchangeable, NH_2), 7.26 (dd, 1H, J = 8.0, 2.0 Hz, H9), 7.42 (d, 1H, J = 2.0 Hz, H7), 7.53 (d, 1H, J = 8.0 Hz, H10); FAB-ms *m*/*z*: 261 (MH^+), 263 ($MH^+ + 2$). Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.96; H, 3.68; N, 10.66.

5-Amino-9-chloro-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (5c) and 5-amino-9-chloro-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitrile (6c). To a preheated solution of **3c** (1.00 g, 3.84 mmol) in dry THF (25 mL) at 60°C was added potassium *tert*-butoxide (470 mg, 4.19 mmol) in one portion and the reaction was then refluxed for 0.5 h. After removal of solvent *in vacuo*, ice water (100 mL) was poured into the residue and the precipitated solid was collected by filtration and chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (4:1) was collected and evaporated *in vacuo*. The yellow solid residue was recrystallized from benzene to give **6c** (230 mg, 23%) as colorless needles. The eluate of *n*-hexane-ethyl acetate (2:1) was collected and evaporated *in vacuo*. The brown solid residue was recrystallized from benzene to give **5c** (120 mg, 12%) as colorless needles. **5c**: m.p. 275–277°C; IR (potassium bromide): 3460, 3300, 3170 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.42 (t, 2H, J = 8.6 Hz, H1), 4.00–5.00 (br, 2H, deuterium oxide exchangeable, NH_2), 4.62 (t, 2H, J = 8.6 Hz, H2), 7.63–8.03 (m, 3H, H7, 8, and 10); EI-ms *m*/*z*: 260 (M^+), 262 ($M^+ + 2$). Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.90; H, 3.61; N, 10.77. **6c**: m.p. 192–193°C; IR (potassium bromide): 3475, 3355 (NH), 2180 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.70 (t, 2H, J = 4.0 Hz, H3), 4.40 (t, 2H, J = 4.0 Hz, H2), 6.22 (br s, 2H, deuterium oxide exchangeable, NH_2), 7.52–7.61 (m, 2H, H7 and 8), 7.65 (d, 1H, J = 1.0 Hz, H10). EI-ms *m*/*z*: 260 (M^+), 262 ($M^+ + 2$). Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 60.02; H, 3.64; N, 10.72.

Ethyl 4-(2-cyano[1]benzofuran-3-yloxy)butyrate (9). To a mixture of **4a** (3.00 g, 18.9 mmol), potassium carbonate (3.70 g, 26.8 mmol), and potassium iodide (150 mg, 0.904 mmol) in dry DMF (90 mL) was added ethyl 4-bromobutyrate (4.40 g, 22.6 mmol), and the reaction was stirred for 1 h at 80°C. The solid was filtered off and the mother liquid was evaporated *in vacuo*. Ice water (150 mL) was poured into the residue, and the mixture was extracted with ethyl acetate (100 mL × 5). The combined organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from *n*-hexane to give **9** (4.50 g, 87%) as colorless needles, m.p. 58°C; IR (potassium bromide): 2230 (CN), 1740 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.27 (t, 3H, J =7.1 Hz, CH_3), 2.11–2.56 (m, 4H, $CH_2CH_2CO_2Et$), 4.11 (t, 2H, J = 6.0 Hz, OCH_2CH_2), 4.50 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.24–7.73 (m, 4H, H4, 5, 6, and 7); FAB-ms *m*/*z*: 274 (MH^+). Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.93; H, 5.53; N, 4.91.

3-(2-Oxo-2,3,4,5-tetrahydrofuran-3-yl)[1]benzofuran-2-carbonitrile (10) and ethyl 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carboxylate (11). To a solution of **9** (3.00 g, 11.0 mmol) in dry THF (70 mL) was added potassium *tert*-butoxide (1.50 g, 13.4 mmol), and the mixture was stirred at room temperature for 0.5 h. After removal of solvent, ice water (100 mL) was poured into the residue, and the mixture was extracted with ethyl acetate (100 mL × 5). The combined organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was

chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (20:1) was collected and evaporated *in vacuo*. The solid residue was recrystallized from *n*-hexane to give **11** (290 mg, 10%) as yellowish green plates. The eluate of *n*-hexane-ethyl acetate (5:1) was collected and evaporated *in vacuo*. The solid residue was recrystallized from cyclohexane to give **10** (930 mg, 37%) as colorless needles. **10**: m.p. 105–108°C; IR (potassium bromide): 2230 (CN), 1755 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 2.66–2.94 (m, 2H, tetrahydrofuran-H4′), 4.05–4.71 (m, 3H, tetrahydrofuran-H3′ and 5′), 7.47–7.67 (m, 4H, H4, 5, 6, and 7); FAB-ms *m*/*z*: 228 (MH^+). Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.87; H, 4.05; N, 6.15. **11**: m.p. 128–129°C; IR (potassium bromide): 3420, 3310 (NH). 1645 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 2.93–3.09 (m, 2H, H3), 4.16–4.46 (m, 4H, 2 × OCH_2), 6.75–7.20 (br, 2H, deuterium oxide exchangeable, NH_2), 7.26–7.71 (m, 4H, H7, 8, 9, and 10); EI-ms *m*/*z*: 273 (M^+). Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.81; H, 5.53; N, 4.91.

5-Chloro-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (12). To a stirred suspension of **5a** (3.00 g, 13.3 mmol) in conc. hydrochloric acid (100 mL) cooled in an ice water bath (0–5°C) was added dropwise sodium nitrite (3.70 g, 53.6 mmol) in water (10 mL) then stirred for 1h. Water (500 mL) was added to the mixture then basified with sodium bicarbonate. The mixture was extracted with ethyl acetate (200 mL × 5). The combined organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (4:1) was evaporated *in vacuo*, and the residue was recrystallized from methanol to give **12** (1.50 g, 46%) as colorless needles, m.p. 220–224°C; ^{1}H-NMR (deuterochloroform): δ 3.61 (t, 2H, J = 9.0 Hz, H1), 4.85 (t, 2H, J = 9.0 Hz, H2), 7.36–7.46 (m, 1H, H9), 7.58–7.70 (m, 2H, H7 and 8), 7.87 (d, 1H, J = 8.0 Hz, H10); FAB-ms *m*/*z*: 246 (MH^+), 248 ($MH^+ + 2$). Anal. Calcd. for $C_{13}H_8ClNO_2$: C, 63.56; H, 3.28; N, 5.70. Found: C, 63.58; H, 3.45; N, 5.71.

5-(2-Hydroxyethylamino)-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (13a). To a solution of **12** (200 mg, 0.814 mmol) in dry 1,4-dioxane (5.0 mL) was added 2-aminoethanol (0.500 mL, 8.28 mmol) the solution was refluxed for 28 h. After removal of solvent *in vacuo*, water (100 mL) was poured into the residue, and the mixture was extracted with diethyl ether (100 mL × 6). The combined organic layer was washed with sat. brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized from acetonitrile to give **13a** (20.0 mg, 9%) as pale brown needles, m.p. 193–194°C; IR (potassium bromide): 3390, 3340 (OH, NH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 3.38 (br s, 1H, deuterium oxide exchangeable, NH or OH), 3.48 (t, 2H, J = 9.0 Hz, H1), 3.75, 3.90 (each br q, each 2H, J = 5.0 Hz, NCH_2CH_2O), 4.74 (t, 2H, J = 9.0 Hz, H2), 5.20 (br s, 1H, deuterium oxide exchangeable, NH or OH), 7.34 (m, 1H, H9), 7.52 (m, 2H, H7 and 8), 7.82 (d, 1H, J = 8.0 Hz, H10); FAB-ms *m*/*z*: 271 (MH^+). Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.76; H, 5.25; N, 10.36.

5-(2-Hydroxyethylsulfanyl)-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (13b) and 1-(2-hydroxyethylsulfanyl)-4-[2-(2-hydroxyethylsulfanyl)ethyl]benzofuro[2,3-*c*]pyridin-3(2*H*)-one (14). To a solution of **12** (200 mg, 0.814 mmol) in dry 1,4-dioxane (5.0 mL) was added 2-sulfanylethanol (0.570 mL, 8.12 mmol) and potassium carbonate (200 mg, 1.45 mmol), and the mixture was then stirred at 80°C for 24 h. After removal of solvent *in vacuo*, water (100 mL) was poured into the residue and the precipitated solid was collected by vacuum filtration and chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (3:2) was evaporated *in vacuo* to give **13b** (80.0 mg, 34%) as a pale yellow viscous oil. The further eluate of *n*-hexane-ethyl acetate (1:1) was evaporated *in vacuo*, and the residue was recrystallized from acetonitrile to give **14** (20.0 mg, 7%) as pale yellow needles. **13b**: IR (chloroform): 3400 (OH) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.58–1.96 (br, 1H, deuterium oxide exchangeable, OH), 3.48 (t, 2H, J = 5.0 Hz, SCH_2), 3.57 (t, 2H, J = 9.0 Hz, H1), 3.98 (t, 2H, J = 5.0 Hz, CH_2O), 4.80 (t, 2H, J = 9.0 Hz, H2), 7.34 (ddd, 1H, J = 8.0, 6.0, 2.0 Hz, H9), 7.58–7.64 (m, 2H, H7 and 8), 7.83 (d, 1H, J = 8.0 Hz, H10); FAB-ms *m*/*z*: 288 (MH^+). Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.77; H, 4.61; N, 4.62. **14**: m.p. 152–153°C; IR (potassium bromide): 3270 br (OH), 2970–2600 (NH), 1630 (CO) cm^{-1}; ^{1}H-NMR (deuterochloroform): δ 1.30–2.30 (br, 2H, deuterium oxide exchangeable, 2 × OH), 2.83–2.96, 3.24–3.44 (each m, each 4H, 3 × SCH_2, C_4-H1'), 3.82, 3.92 (each t, each 2H, J = 6.0 Hz, 5.0 Hz, 2 × OCH_2), 7.34–7.45 (m, 1H, H6), 7.59–7.67 (m, 2H, H7 and 8), 8.02 (d, 1H, J = 8.0 Hz, H5); FAB-ms *m*/*z*: 366 (MH^+). Anal. Calcd. for $C_{17}H_{19}NO_4S_2$: C, 55.87; H, 5.24; N, 3.83. Found: C, 55.69; H, 5.22; N, 3.74.

5-Morpholino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridine (15). A solution of **12** (200 mg, 0.814 mmol) in morpholine (5.0 mL) was heated at 120°C for 137 h. After removal of excess morpholine *in vacuo*, ice water (100 mL) was poured into the residue, the precipitated solid was collected by vacuum filtration and chromatographed on silica gel. The eluate of *n*-hexane-ethyl acetate (5:1) was evaporated *in vacuo*, and the residue was recrystallized from acetonitrile to give **15** (110 mg, 46%) as colorless prisms, m.p. 197–199°C; ^{1}H-NMR (deuterochloroform): δ 3.53 (t, 2H, J = 9.0 Hz, H1), 3.81, 3.90 (each m, each 4H, morpholine-H), 4.75 (t, 2H, J = 9.0 Hz, H2), 7.32–7.41 (m, 1H, H9), 7.54–7.59 (m, 2H, H7 and 8), 7.84 (d, 1H, J = 8.0 Hz, H10); ESI-ms *m*/*z*: 297 (MH^+). Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.92; H, 5.46; N, 9.42.

Acknowledgments. The authors are grateful to the SC-NMR Laboratory of Okayama University for 200 MHz ^{1}H-NMR experiments. They also thank Dr. K. L. Kirk (NIDDK, NIH) for helpful suggestions.

REFERENCES AND NOTES

[1] For recent reports, see (a) Okuda, K.; Zhang, Y.-X.; Ohtomo, H.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 369; (b) Okuda, K.; Deguchi, H.; Kashino, S.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 685.

[2] Hirota, T.; Matsushita, T.; Sasaki, K.; Kashino, S. Heterocycles 1995, 41, 2565.

[3] Sasaki, K.; Rouf, A. S. S.; Hirota, T. J Heterocycl Chem 1996, 33, 49.

[4] Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. Heterocycles 2001, 55, 741.

[5] Okuda, K.; Yoshida, M.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 363.

[6] Snape, T. J. Chem Soc Rev 2008, 37, 2452.

[7] Erickson, W. R.; McKennon, M. J. Tetrahedron Lett 2000, 41, 4541.

[8] Kimbaris, A.; Cobb, J.; Tsakonas, G.; Varvounis, G. Tetrahedron 2004, 60, 8807.

[9] Mitchell, L. H.; Barvian, N. C. Tetrahedron Lett 2004, 45, 5669.

[10] Snape, T. J. Synlett 2008, 2689.

[11] Bryant, R.; Haslam, D. L. J Chem Soc 1965, 2361.

[12] Philipp, A.; Jirkovsky, I.; Martel, R. U. S. Pat. 4,420,476, 1983.

[13] Yokoo, H.; Seki, M.; Kojima, K. Jpn Kokai Tokkyo Koho 60011466, 1985.

[14] Okuda, K.; Watanabe, N.; Hirota, T.; Sasaki, K. Tetrahedron Lett 2010, 51, 903.

[15] We have experienced a similar type of dihydrofuran ring cleavage reaction of fused 6-halo-2,3-dihydrofuro[2,3-*b*]pyridines recently. See: Okuda, K.; Deguchi, H.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 755.

[16] Compound **4a** existed as an enol form judged from ^{1}H-NMR in DMSO-d_6 but as a keto-enol tautomeric mixtures based on ^{1}H-NMR in deuterochloroform. This assumption was also supported by characteristic absorption in its IR spectrum (chloroform solution vs. potassium bromide tablet). For **4b** and **4c**, we only measured ^{1}H-NMR in DMSO-d_6 and IR in potassium bromide tablet.