Polycyclic *N*-Heterocyclic Compounds. Part 63[1] Improved Synthesis of 5-Amino-1,2-dihydrofuro[2,3-*c*]isoquinolines *via* Truce–Smiles Rearrangement and Subsequent Formation to Furo[2,3-*c*]isoquinoline

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An improved synthesis of 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinoline has been achieved using a slight modification of reaction conditions for the Truce–Smiles rearrangement. Acid treatment of the obtained 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinolines gave unexpected ring-opened spiro ring compounds. The previously unreported parent compound, furo[2,3-*c*]isoquinoline, was also synthesized.

Key words Truce–Smiles rearrangement; furo[2,3-*c*]isoquinoline; furo[2,3-*b*]pyridine; heterocycle; spiro[cyclopropane-(1,4′)-isoquinoline]

Formation of carbon–carbon (C–C) bonds is a central issue in synthetic organic chemistry. In this regard, the Truce–Smiles rearrangement is among those useful rearrangement reactions that provide access to complex structures from simple precursors through formation of new C–C bonds.[2—6)]

We have previously reported the application of the Truce–Smiles rearrangement for the synthesis of many aromatic fused dihydrothieno (or dihydrofuro)naphthyridines (**1**) in one step from cyanopyridines having a 3-cyanopropoxy group adjacent to cyano group (**2**). Thus, base-mediated Truce–Smiles rearrangement of **2** followed by intramolecular cyclization (Chart 1) produces **1** in moderate to good yields.[7—10)] Some of these products and their chemically modified derivatives showed promising bronchodilatory activity in a primary *in vitro* assay (relaxation of tracheal contraction induced by carbamylcholine chloride).[11)] As an extension of this work, we sought to expand this rearrangement reaction system to 2-(3-cyanopropoxy)benzonitrile (**3a**) as a route to 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinoline (**4a**). This transformation was successful but the product yield was low (14%)[12)] because **3a** is not activated for nucleophilic reaction compared to **2**. As is well established, the key step of the Truce–Smiles rearrangement is the *ipso* attack of an incoming nucleophile.[13)] In order to apply this reaction for further syntheses of heterocycles with potential pharmaceutical applications, including bronchodilatory activity, we initiated a study of conditions designed to improve this reaction step. Here we report the optimization of reaction conditions and the successful application of this reaction using 5-substituted 2-(3-cyanopropoxy)benzonitriles (**3a**—**c**) as substrates.

Results and Discussion

Substrate compounds **3b** and **3c** were prepared as shown in Chart 2. First, 5-chloro-2-hydroxybenzoic and 5-nitro-2-hydroxybenzoic acid (**5b**, **5c**) were transformed to 5-chloro-2-(3-cyanopropoxy)benzoic acid and 2-(3-cyanopropoxy)-5-nitro-benzoic acid (**8b**, **8c**), respectively. Next, **8b** and **8c** were activated with phosphoryl chloride and then treated with liquid ammonia to give the carboxamide derivatives (**9b**, **9c**). Dehydration of **9b** and **9c** with phosphoryl chloride gave the desired dinitriles (**3b**, **3c**).

The initial reaction of **3a** with potassium *tert*-butoxide in *N*,*N*-dimethylformamide (DMF) at room temperature produced **4a**, albeit in only 14% yield (Table 1, run 1).[12)] Changing the solvent from DMF to dioxane did not significantly improve the product yield (17%, run 2). However, addition of potassium *tert*-butoxide around 95 °C in one portion to the reaction solution and raising the reaction temperature to reflux for 1 h increased the yield of **4a** to 60% (run 3). Using NaH as base gave no further improvement in yield compared to potassium *tert*-butoxide (runs 4 and 5). We then turned our attention to reactions of **3b** which has a Cl substituent, a relatively weak electron withdrawing group. As with **3a**, the reaction at room temperature in dioxane for **3b** gave a poor result (run 6). However, under reflux **4b** was formed in 83% yield (run 7). From these results, we expected that **3c** would be a more favorable substrate under these reaction conditions because the Truce–Smiles rearrangement is known to occur

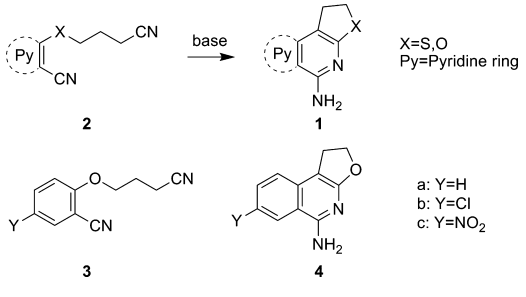

Chart 1. Substrates (**2**, **3**) and Their Rearranged Products (**1**, **4**)

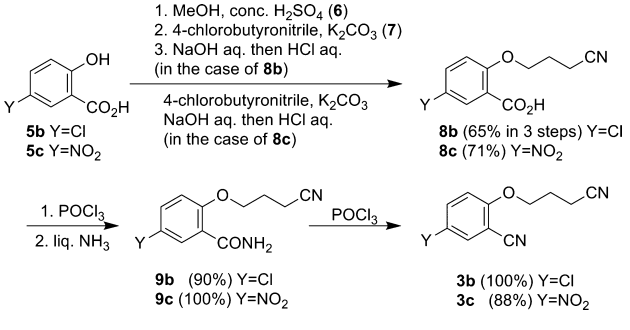

Chart 2. Preparation of **3b** and **3c**

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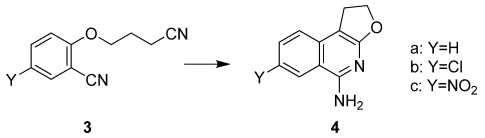
Table 1. Reaction of Dinitriles **3** with Bases to Give **4**



3 **4**

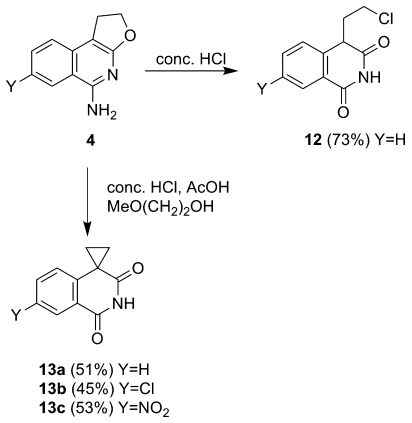
Run	Compd.	Base[a)]	Solvent	Temperature	Time (h)	Yield (%)
1	**3a**	*tert*-BuOK	DMF	r.t.	4	14[12)]
2	**3a**	*tert*-BuOK	Dioxane	r.t.	24	17
3	**3a**	*tert*-BuOK	Dioxane	Reflux[b)]	1	60
4	**3a**	NaH	Dioxane	r.t.	24	N.R.
5	**3a**	NaH	Dioxane	Reflux[c)]	72	42
6	**3b**	*tert*-BuOK	Dioxane	r.t.	22	18
7	**3b**	*tert*-BuOK	Dioxane	Reflux[b)]	0.1	83
8	**3c**	*tert*-BuOK	DMF	r.t.	0.5	17
9	**3c**	*tert*-BuOK	Dioxane	r.t.	0.5	24
10	**3c**	*tert*-BuOK	Dioxane	Reflux[b)]	0.1	Trace
11	**3c**	NaH	Dioxane	r.t.	24	N.R.
12	**3c**	NaH	Dioxane	Reflux[c)]	24	N.R.
13	**3c**	NaOEt	Dioxane	r.t.	2	[d)]

a) 2 eq base was used except for run 13 (1.2 eq base). *b*) Base was added around 95 °C in one portion to the reaction solution then refluxed. *c*) Base was added at room temperature to the reaction solution then refluxed. *d*) 2-Ethoxy-5-nitrobenzonitrile (**10**) was obtained (51%). r.t.: room temperature. N.R.: no reaction.

readily on reactants having the strong electron withdrawing nitro group.[13)] However, reaction of **3c** with potassium *tert*-butoxide in dioxane under reflux condition was unsuccessful. Many spots on TLC analysis indicated that these reaction conditions were too harsh for an activated substrate such as **3c** (run 10). Reaction under milder conditions (room temperature) either in DMF or in dioxane gave **4c**, but in relatively low yield (17 and 24%, runs 8 and 9). When **3c** was allowed to react with sodium ethoxide as the base, the 3-cyanopropoxy group was displaced by ethoxide to give 2-ethoxy-5-nitrobenzonitrile (**10**, 51%, run 13). This shows that the bulky *tert*-butoxide is a better base for this reaction.

Although several derivatives containing the furo[2,3-*c*]isoquinoline ring system have been already synthesized,[14—17)] the parent ring skeleton, unsubstituted furo[2,3-*c*]isoquinoline (**11**), has not been reported. We therefore attempted to execute sequential deamination and aromatization of **4a** to give **11**. Our initial synthetic strategy appeared to be quite straightforward. Thus, we expected that **11** could be prepared by the following sequence of reactions; 1) acid hydrolysis of the amino group of **4a** to the corresponding lactam, 2) chlorination of the lactam carbonyl group with phosphoryl chloride, 3) dechlorination by catalytic hydrogenation, and 4) aromatization with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ).

We encountered immediate problems with this approach. When **4a** was heated with conc. hydrochloric acid, an unexpected furan ring opening occurred to yield 4-(2-chloroethyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (**12**) in 73% yield (Chart 3).[18)] We then tried hydrolysis of **10a** under milder condition using conc. hydrochloric acid and acetic acid in 2-methoxyethanol. Under these conditions the furan ring opened again and a rearranged product, spiro[cyclopropane-1,4′(1′*H*)-isoquinoline]-1′,3′(2′*H*)-dione (**13a**)[19)] was obtained. The presence of the cyclopropane ring is shown by a 1.66 and 2.16 ppm upfield shift of the aliphatic protons in the ^{1}H-NMR spectrum of **13a**. A possible proposed reaction mechanism of **4** to **12** and **13a** is shown



4 **12** (73%) Y=H

13a (51%) Y=H
13b (45%) Y=Cl
13c (53%) Y=NO_2

Chart 3. Reaction of **4** with Acid

in Chart 4. We have previously observed this sort of rearrangement in our laboratory,[10)] in that a similar spiro compound spiro[cyclopropane-1,5′(6′*H*)-[1,7]naphthyridine]-6′,8′(7′*H*)-dione was obtained from 5-amino-1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine on treatment with conc. hydrochloric acid.

To explore the generality of this reaction, compounds **4b** and **4c** were subjected to the same reaction conditions. The corresponding spiro derivatives **13b** and **13c** were produced in moderate yield.

Since we were unable to hydrolyze the amino group of **4** to produce the desired lactam, we next tried to access the corresponding chloro derivative by a diazotization reaction of **4** with sodium nitrite in conc. hydrochloric acid (Chart 5). This in fact produced the desired 5-chloro derivative **14a**, but in only 8% yield. Low yields were also obtained in similar reactions with **14b** and **14c** (5% and 15% yield, respectively). It is possible that the poor yields were due to low solubility of **4** in conc. hydrochloric acid. Unacceptably low yields for **14a** and **14b** prompted us to examine another diazotization procedure. Somewhat better results were obtained in the reaction

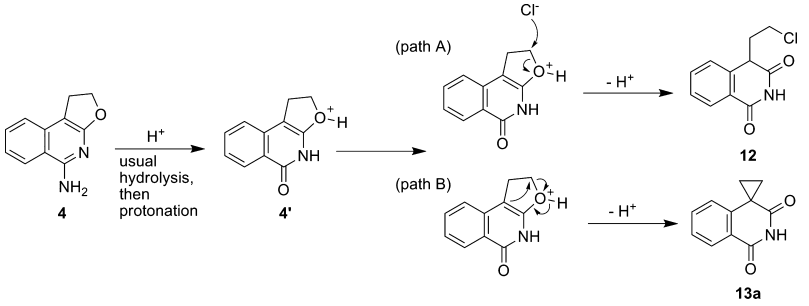


Chart 4. Mechanistic Proposal for Formation of **12** and **13**

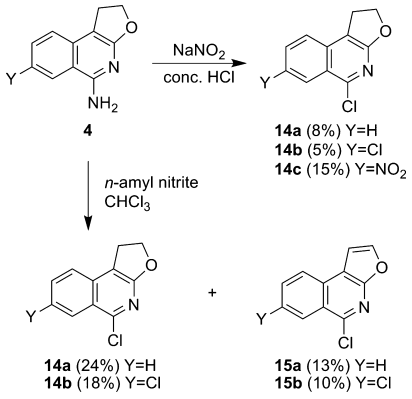


Chart 5. Deaminochlorination of **4**

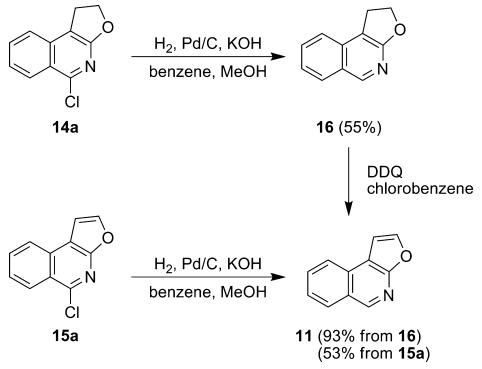


Chart 6. Synthesis of Furo[2,3-*c*]isoquinoline (**11**)

of **4a** with *n*-amyl nitrite in chloroform.[20,21] This gave two products, 5-chloro derivative **14a** and the product of its dehydrogenation **15a** in 24% and 13% yield, respectively. Reaction of **4b** under these conditions gave **14b** and **15b** in 18% and 10% yield, respectively.

Finally, the parent skeleton, furo[2,3-*c*]isoquinoline **11** was synthesized by using the above two products **14a** and **15a**, as shown in Chart 6. Catalytic hydrogenation of **14a** gave dechlorinated compound **16** in 55% yield. This was treated with DDQ to give desired parent skeleton **11** in 93% yield. Dechlorination of **15a** with catalytic hydrogenation also gave **11** in 53% yield.

In summary, we have developed an improved method for the synthesis of 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinoline (**4**) based on the Truce–Smiles rearrangement. Acid treatment of **4** gave unexpected ring-opened spiro ring compounds. The previously unreported parent compound, furo[2,3-*c*]isoquinoline (**11**), was also synthesized. We are currently exploring the biological properties of the products with the goal of developing new pharmaceutical agents.

Experimental

General 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 FAB-mass and EI-mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol or glycerol was used as the matrix. The IR spectra were recorded on a Japan Spectroscopic diffraction grating A-102 or FT/IR-200 spectrophotometer with KBr and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz or Hitachi R-1500 instrument operating at 60 MHz 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; quin, quintet; 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).

Methyl 5-Chloro-2-hydroxybenzoate (6) To a solution of 5-chloro-2-hydroxybenzoic acid (**5b**, 1.00 g, 5.79 mmol) in dry methanol (1.0 ml) was added conc. H_2SO_4 (600 mg, 6.12 mmol) and the mixture was refluxed for 4 h. After addition of water, the mixture was extracted with diethyl ether (10 ml). The combined organic layer was washed with water (10 ml×3), saturated $KHCO_3$ aq. solution, and saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from *n*-hexane to give **6** (900 mg, 83%) as colorless needles, mp 46—47 °C (lit.[22] 44—46 °C). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.96 (3H, s, OCH_3), 6.93 (1H, d, J=9.1 Hz, H-3), 7.41 (1H, dd, J=9.1, 2.6 Hz, H-4), 7.81 (1H, d, J=2.6 Hz, H-6), 10.66 (1H, br s, D_2O exchangeable OH). IR (KBr) cm^{-1}: 3130, (OH), 1660 (CO). EI-MS *m/z*: 186 (M^+), 188 (M^++2). *Anal.* Calcd for $C_8H_7ClO_3$: C, 51.49; H, 3.78. Found: C, 51.60; H, 3.77.

Methyl 5-Chloro-2-(3-cyanopropoxy)benzoate (7) To a solution of **6** (330 mg, 1.77 mmol) in dry DMF (1.0 ml) were added 4-chlorobutyronitrile (274 mg, 2.66 mmol) and K_2CO_3 (366 mg, 2.66 mmol) and the mixture was refluxed for 5 h. After addition of ice water (90 ml), the mixture was extracted with ethyl acetate (100 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of benzene was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **7** (368 mg, 82%) as colorless needles, mp 56—57 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.23 (2H, br quin, J=6.0 Hz, H-2′), 2.72 (2H, t, J=6.0 Hz, H-3′), 3.88 (3H, s, OCH_3), 4.14 (2H, t, J=6.0 Hz, H-1′), 6.90 (1H, d, J=8.9 Hz, H-3), 7.41 (1H, dd, J=8.9, 2.6 Hz, H-4), 7.80 (1H, d, J=2.6 Hz, H-6). IR (KBr) cm^{-1}: 2235 (CN), 1705 (CO). FAB-MS *m/z*: 254 (MH^+), 256 (MH^++2). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.65; H, 4.78; N, 5.48.

5-Chloro-2-(3-cyanopropoxy)benzoic Acid (8b) To a solution of **7** (1.00 g, 3.94 mmol) in dioxane (20 ml) was added 1 N NaOH (20 ml) and the solution was stirred at room temperature for 2 h. The reaction mixture was acidified with 1 N HCl and then extracted with ethyl acetate (20 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from ethyl acetate–*n*-hexane to give **8b** (900 mg, 95%) as colorless needles, mp 94—95 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.28 (2H,, br quin, J=6.0 Hz, H-2′), 2.70 (2H, t, J=6.0 Hz, H-3′), 4.24 (2H, t, J=6.0 Hz, H-1′), 6.96 (1H, d, J=8.8 Hz, H-3), 7.51 (1H, dd, J=8.8, 2.6 Hz, H-4), 8.02 (1H, d, J=2.6 Hz, H-6), 9.92 (1H, br s, D_2O exchangeable, OH). IR (KBr) cm^{-1}: 3430 (OH),

2245 (CN), 1700 (CO). FAB-MS *m/z*: 240 (MH^+), 242 (MH^++2). *Anal.* Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.07; H, 4.36; N, 5.77.

2-(3-Cyanopropoxy)-5-nitrobenzoic Acid (8c) To a solution of 2-hydroxy-5-nitrobenzoic acid (**5c**, 200 mg, 1.09 mmol) in dry DMF (5.0 ml) were added 4-chlorobutyronitrile (451 mg, 4.36 mmol) and K_2CO_3 (300 mg, 2.18 mmol), and the reaction mixture was refluxed for 1.5 h. After cooling of the reaction mixture to room temperature, ice water (25 ml) and 1 N NaOH (10 ml) were added and the mixture was stirred at room temperature for 1 h. The resulting solution was acidified with 1 N HCl and extracted with ethyl acetate (10 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from ethanol to give **8c** (193 mg, 71%) as colorless needles, mp 135—137 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.24 (2H, quin, J=6.3 Hz, H-2′), 2.61 (2H, t, J=6.3 Hz, H-3′), 4.58 (2H, t, J=6.3 Hz, H-1′), 7.10 (1H, d, J=9.2 Hz, H-3), 8.36 (1H, dd, J=9.2, 2.7 Hz, H-4), 8.77 (1H, d, J=2.7 Hz, H-6), 11.33 (1H, br s, D_2O exchangeable, OH). IR (KBr) cm^{-1}: 3430 (OH), 2260 (CN), 1675 (CO), 1515, 1340 (NO_2). FAB-MS *m/z*: 251 (MH^+). *Anal.* Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.75; H, 4.17; N, 11.43.

5-Chloro-2-(3-cyanopropoxy)benzamide (9b) Compound **8b** (1.00 g, 4.17 mmol) in $POCl_3$ (6.40 g, 41.8 mmol) was refluxed for 4 h. After evaporation of excess $POCl_3$, dry toluene (10 ml) was added to the residue then evaporated again *in vacuo* twice. The residue was cooled with dry ice–acetone and liq. NH_3 (*ca.* 50 ml) was added. The mixture was allowed to stand for one night and saturated brine was added to the mixture. The resulting solid was washed with water. The precipitate was filtered *in vacuo* and then recrystallized from ethanol–*n*-hexane to give **9b** (900 mg, 90%) as colorless needles, mp 120—121 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.10—2.71 (4H, m, H-2′, 3′), 4.26 (2H, t, J=5.6 Hz, H-1′), 6.46 (2H, br s, D_2O exchangeable, NH_2), 6.92 (1H, d, J=8.8 Hz, H-3), 7.42 (1H, dd, J=8.8, 2.6 Hz, H-4), 8.11 (1H, d, J=2.6 Hz, H-6). IR (KBr) cm^{-1}: 3385, 3190 (NH), 2250 (CN), 1635 (CO). FAB-MS *m/z*: 239 (MH^+), 241 (MH^++2). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.30; H, 4.64; N, 11.74.

2-(3-Cyanopropoxy)-5-nitrobenzamide (9c) To a solution of **8c** (5.00 g, 20.0 mmol) in dry dioxane (50 ml) was added $POCl_3$ (9.18 g, 60.0 mmol) and the mixture was then refluxed for 4 h. After evaporation of excess $POCl_3$, dry toluene (20 ml) was added to the residue then evaporated again *in vacuo* three times. The residue was cooled with dry ice–acetone and liq. NH_3 (*ca.* 200 ml) was added. The mixture was allowed to stand for one night and saturated brine was added to the mixture. The resulting solid was washed with water. The precipitate was filtered *in vacuo* and extracted with acetone. The combined acetone extracts were evaporated. The resulting residue was recrystallized from ethyl acetate to give **9c** (4.98 g, 100%) as pale brown scales, mp 170—172 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.15 (2H, quin, J=6.3 Hz, H-2′), 2.69 (2H, t, J=6.3 Hz, H-3′), 4.30 (2H, t, J=6.3 Hz, H-1′), 7.38 (1H, d, J=9.2 Hz, H-3), 7.82 (2H, br s, D_2O exchangeable, NH_2), 8.34 (1H, dd, J=9.2, 2.7 Hz, H-4), 8.47 (1H, d, J=2.7 Hz, H-6). IR (KBr) cm^{-1}: 3485, 3190 (NH), 2260 (CN), 1670 (CO), 1510, 1345 (NO_2). FAB-MS *m/z*: 250 (MH^+). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.09; H, 4.51; N, 16.83.

5-Chloro-2-(3-cyanopropoxy)benzonitrile (3b) To a solution of **9b** (200 mg, 0.838 mmol) in dry $CHCl_3$ (2.0 ml) was added $POCl_3$ (1.29 g, 8.41 mmol) and the mixture was then refluxed for 2 h. After evaporation of $CHCl_3$ and excess $POCl_3$, ice water (15 ml) was added to the residue. The resulting precipitate was filtered, washed with water, and the residue was recrystallized from diethyl ether to give **3b** (185 mg, 100%) as colorless needles, mp 57—58 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.17—2.42 (2H, m, H-2′), 2.70 (2H, t, J=5.6 Hz, H-3′), 4.21 (2H, t, J=5.6 Hz, H-1′), 6.95 (1H, d, J=9.7 Hz, H-3), 7.42—7.63 (2H, m, H-4, H-6). IR (KBr) cm^{-1}: 2245, 2235 (CN). FAB-MS *m/z*: 221 (MH^+), 223 (MH^++2). *Anal.* Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.76; H, 4.23; N, 12.81.

2-(3-Cyanopropoxy)-5-nitrobenzonitrile (3c) To a solution of **9c** (1.05 g, 4.21 mol) in dry dioxane (20 ml) was added $POCl_3$ (6.46 g, 42.1 mmol) and the mixture was then refluxed for 1 h. After evaporation of dioxane and excess $POCl_3$, ice water (500 ml) was added to the residue. The resulting mixture was neutralized with $NaHCO_3$ (pH 7). The solution was extracted with ethyl acetate (100 ml×3) and the combined organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from ethanol to give **3c** (860 mg, 88%) as pale yellow needles, mp 84—86 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.09—2.17 (2H, m, H-2′), 2.69 (2H, t, J=6.5 Hz, H-3′), 4.38 (2H, t, J=6.5 Hz, H-1′), 7.50 (1H, d, J=9.3 Hz, H-3), 8.52 (1H, dd, J=9.3, 2.8 Hz, H-4), 8.71 (1H, d, J=2.8 Hz, H-6). IR (KBr) cm^{-1}: 2270, 2260 (CN), 1525, 1345 (NO_2). EI-MS *m/z*: 231 (M^+). *Anal.* Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.21; H, 4.10; N, 17.90.

5-Amino-1,2-dihydrofuro[2,3-*c*]isoquinoline (4a) To a solution of **3a**[12] (1.00 g, 5.37 mmol) in dry dioxane (30 ml) around 95 °C was added *tert*-BuOK (1.20 g, 10.8 mmol) in one portion under stirring. Solid precipitated during the reaction after about 1 h, at which time the mixture was cooled to room temperature. After evaporation of solvent, the residue was washed with ice water (300 ml) and then filtered. The mother liquid was extracted with ethyl acetate (100 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue and the above precipitate were combined and recrystallized from acetone to give **4a** (600 mg, 60%) as pale brown prisms. All analytical data (mp, IR, ^{1}H-NMR, MS, and EA) were in good agreement with literature values.[12]

5-Amino-7-chlorofuro[2,3-*c*]isoquinoline (4b) To a solution of **3b** (300 mg, 1.36 mmol) in dry dioxane (3.0 ml) around 95 °C was added *tert*-BuOK (305 mg, 2.72 mmol) in one portion under stirring. Solid precipitated during the reaction after about 0.1 h, at which time the mixture was cooled to room temperature. After evaporation of solvent, the residue was washed with ice water (30 ml) and then filtered. The mother liquid was extracted with ethyl acetate (10 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue and the above precipitate were combined and recrystallized from ethyl acetate to give **4b** (250 mg, 83%) as pale brown needles, mp 254—255 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.32 (2H, t, J=8.8 Hz, H-1), 4.72 (2H, t, J=8.8 Hz, H-2), 5.16 (2H, br s, D_2O exchangeable, NH_2), 7.36 (1H, d, J=8.9 Hz, H-9), 7.46 (1H, dd, J=8.9, 2.0 Hz, H-8), 7.70 (1H, d, J=2.0 Hz, H-6). IR (KBr) cm^{-1}: 3490, 3395 (NH). FAB-MS *m/z*: 221 (MH^+), 223 (MH^++2). *Anal.* Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.90; H, 4.28; N, 12.79.

5-Amino-7-nitrofuro[2,3-*c*]isoquinoline (4c) To a solution of **3c** (3.01 g, 13.0 mmol) in dry dioxane (50 ml) was added *tert*-BuOK (2.91 g, 25.9 mmol) and the mixture was stirred for 0.5 h at room temperature. After evaporation of solvent *in vacuo*, the residue was treated with hot acetone. The combined acetone extracts were evaporated. The resulting residue was recrystallized from acetone to give **4c** (720 mg, 24%) as deep red needles, mp 271—273 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.24 (2H, t, J=8.6 Hz, H-1), 4.66 (2H, t, J=8.6 Hz, H-2), 7.44 (1H, d, J=9.2 Hz, H-9) 7.69 (2H, br s, D_2O exchangeable, NH_2), 8.19 (1H, dd, J=9.2, 2.2 Hz, H-8), 9.21 (1H, d, J=2.2 Hz, H-6). IR (KBr) cm^{-1}: 3470, 3300 (NH), 1480, 1310 (NO_2). FAB-MS *m/z*: 232 (MH^+). *Anal.* Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.01; H, 3.90; N, 18.02.

2-Ethoxy-5-nitrobenzonitrile (10) To a solution of **3c** (200 mg, 0.865 mmol) in dry dioxane (5.0 ml) was added EtONa (70.0 mg, 1.03 mmol) and the mixture was stirred for 2 h at room temperature After evaporation of solvent, water (25 ml) was added to the residue and the aqueous solution was then extracted with ethyl acetate (10 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was chromatographed on silica gel, and the eluate of cyclohexane–ethyl acetate (9 : 1 to 4 : 1) was collected and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give **10** (84.0 mg, 51%) as colorless needles, mp 101—102 °C (lit.[23] 94 °C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.56 (3H, t, J=7.0 Hz, CH_3), 4.30 (2H, q, J=7.0 Hz, OCH_2), 7.07 (1H, d, J=9.2 Hz, H-3), 8.43 (1H, dd, J=9.2, 2.7 Hz, H-4), 8.49 (1H, d, J=2.7 Hz, H-6). IR (KBr) cm^{-1}: 2245 (CN), 1515, 1340 (NO_2). FAB-MS *m/z*: 193 (MH^+). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.19; H, 4.26; N, 14.57.

4-(2-Chloroethyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (12) A solution of **4a** (500 mg, 2.69 mmol) in conc. HCl (50 ml) was refluxed for 4 h. After cooling the reaction mixture to room temperature, it was made basic with $NaHCO_3$. The precipitated solid was filtered off and the mother liquid was extracted with ethyl acetate (50 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue and the above solid were combined then recrystallized from ethyl acetate to give **12** (440 mg, 73%) as colorless prisms, mp 168—170 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.50 (2H, td, J=6.4, 6.4 Hz, H-1′), 3.50—3.77 (2H, m, H-2′), 4.11 (1H, t, J=6.4 Hz, H-4), 7.41 (1H, d, J=7.5 Hz, H-5), 7.50 (1H, m, H-7), 7.69 (1H, m, H-6), 8.24 (1H, dd, J=7.5, 1.4 Hz, H-8), 8.13—8.40 (1H, br s, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3180, 3085 (NH), 1690, 1675, (CO). FAB-MS *m/z*: 224 (MH^+), 226 (MH^++2). *Anal.* Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.18; H, 4.64; N, 6.26.

General Procedure for Preparation of 13 To a solution of **4** (200 mg) in 2-methoxyethanol (10 ml) were added acetic acid (4.0 ml) and conc. HCl (2.0 ml) and the reaction mixture was refluxed for the appropriate time. After cooling, $NaHCO_3$ was added to the reaction mixture and the aqueous solution was extracted with ethyl acetate (30 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give **13**.

Spiro[cyclopropane-1,4′(1′*H*)-isoquinoline]-1′,3′(2′*H*)-dione (13a) Refluxed for 8 h. Colorless prisms **13a** (103 mg, 51%), mp 215—217 °C (lit.[19] 206—207 °C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.63—1.69 and 2.13—2.19 (each 2H, each m, H-cyclopropane), 6.84 (1H, br d, J=8.0 Hz, H-5′), 7.41 (1H, br t, J=8.0 Hz, H-7′), 7.61 (1H, td, J=8.0, 1.4 Hz, H-6′), 8.26 (1H, dd, J=8.0, 1.4 Hz, H-8′), 8.42 (1H, br s, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3180, 3080 (NH), 1710, 1670 (CO). FAB-MS *m/z*: 188 (MH^+). *Anal.* Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.33; H, 4.94; N, 7.32.

7′-Chlorospiro[cyclopropane-1,4′(1′*H*)-isoquinoline]-1′,3′(2′*H*)-dione (13b) Refluxed for 6 h. Colorless needles **13b** (90.0 mg, 45%), mp 232—233 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.68—1.74 and 1.88—1.94 (each 2H, each m, H-cyclopropane), 7.12 (1H, d, J=8.5 Hz, H-5′), 7.69 (1H, dd, J=8.5, 2.4 Hz, H-6′), 7.98 (1H, d, J=2.4 Hz, H-8′), 11.65 (1H, br s, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3195, 3075 (NH), 1700 (CO). FAB-MS *m/z*: 222 (MH^+), 224 (MH^++2). *Anal.* Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.61; H, 3.83; N, 6.23.

7′-Nitrospiro[cyclopropane-1,4′(1′*H*)-isoquinoline]-1′,3′(2′*H*)-dione (13c) Refluxed for 23 h. Pale red prisms **13c** (106 mg, 53%), mp >300 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.84—1.90, 2.02—2.08 (each 2H, each m, H-cyclopropane), 7.36 (1H, d, J=8.8 Hz, H-5′), 8.40 (1H, J=8.8, 2.6 Hz, H-6′), 8.70 (1H, d, J=2.6 Hz, H-8′), 11.88 (1H, br s, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3200, 3090 (NH), 1710, 1690 (CO), 1530, 1345 (NO_2). FAB-MS *m/z*: 233 (MH^+). *Anal.* Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06. Found: C, 56.81; H, 3.52; N, 12.06.

5-Chloro-1,2-dihydrofuro[2,3-*c*]isoquinoline (14a) To a suspension of **4a** (500 mg, 2.69 mmol) in conc. HCl (100 ml) under ice water cooling was added a solution of $NaNO_2$ (740 mg, 10.8 mmol, 1.8 ml of water) dropwise with stirring. The end point of the reaction was confirmed with KI-starch paper at which time the solution was basified with $NaHCO_3$. The mixture was extracted with ethyl acetate (100 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was chromatographed on silica gel and the eluate of petroleum ether–diethyl ether (9 : 1) was evaporated. The residue was recrystallized from petroleum ether to give **14a** (45.0 mg, 8%) as pale yellow feathers, mp 111—113 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.50 (2H, t, J=9.0 Hz, H-1), 4.83 (2H, t, J= 9.0 Hz, H-2), 7.43 (1H, m, H-7), 7.54—7.71 (2H, m, H-8, 9), 8.26 (1H, br d, J=8.7 Hz, H-6). FAB-MS *m/z*: 206 (MH^+), 208 (MH^++2). *Anal.* Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92; N, 6.81. Found: C, 64.22; H, 4.01; N, 6.72.

5,7-Dichloro-1,2-dihydrofuro[2,3-*c*]isoquinoline (14b) To a suspension of **4b** (200 mg, 0.906 mmol) in conc. HCl (100 ml) under ice water cooling was added a solution of $NaNO_2$ (251 mg, 3.64 mmol, 0.9 ml of water) dropwise with stirring. The end point of the reaction was confirmed with KI-starch paper at which time the solution was basified with $NaHCO_3$. The mixture was extracted with ethyl acetate (30 ml×3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of petroleum ether–diethyl ether (9 : 1) was evaporated and the residue was recrystallized from ethanol to give **14b** (11.0 mg, 5%) as pale yellow feathers, mp 182—183 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.49 (2H, t, J=8.9 Hz, H-1), 4.83 (2H, t, J=8.9 Hz, H-2), 7.51 (1H, d, J=8.7 Hz, H-9), 7.60 (1H, dd, J=8.7, 1.4 Hz, H-8), 8.24 (1H, d, J=1.4 Hz, H-6). FAB-MS *m/z*: 240 (MH^+), 242 (MH^++2), 244 (MH^++4). *Anal.* Calcd for $C_{11}H_7Cl_2NO$: C, 55.03; H, 2.94; N, 5.83. Found: C, 55.04; H, 3.07; N, 5.80.

5-Chloro-7-nitro-1,2-dihydrofuro[2,3-*c*]isoquinoline (14c) To a suspension of **4c** (1.81 g, 7.83 mmol) in conc. HCl (300 ml) under ice water cooling was added a solution of $NaNO_2$ (2.53 g, 36.7 mmol, 9.0 ml of water) dropwise. The workup of the reaction was carried out as described in **14a**, and the obtained residue was chromatographed on silica gel. The eluate of cyclohexane–ethyl acetate (4 : 1) was evaporated and the residue was recrystallized from benzene to give **14c** (290 mg, 15%) as yellow feathers, mp 243—244 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.54 (2H, t, J=9.0 Hz, H-1), 4.88 (2H, t, J=9.0 Hz, H-2), 7.97 (1H, d, J=9.0 Hz, H-9), 8.45 (1H, dd, J=9.0, 2.0 Hz, H-8), 8.97 (1H, d, J=2.0 Hz, H-6). IR (KBr) cm^{-1}: 1500, 1335 (NO_2). FAB-MS *m/z*: 251 (MH^+), 253 (MH^++2). *Anal.* Calcd for $C_{11}H_7ClN_2O_3$: C, 52.71; H, 2.82; N, 11.18. Found: C, 52.84; H, 2.91; N, 11.26.

5-Chloro-1,2-dihydrofuro[2,3-*c*]isoquinoline (14a) and 5-Chlorofuro-[2,3-*c*]isoquinoline (15a) To a solution of **4a** (180 mg, 0.97 mmol) in dry $CHCl_3$ (50 ml) was added *n*-amyl nitrite (446 mg, 3.88 mmol) and the mixture was then refluxed for 0.5 h. After cooling, the solution was evaporated *in vacuo* and the residue was chromatographed on silica gel. An early fraction eluted with petroleum ether–diethyl ether (9 : 1) was evaporated and the residue was recrystallized from petroleum ether to give **15a** (26.0 mg, 13%) as pale red feathers, mp 109—111 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.23 (1H, d, J=2.3 Hz, H-1), 7.67 (1H, m, H-7), 7.81 (1H, J=2.3 Hz, H-2), 7.85 (1H, m, H-8), 8.15 (1H, dd, J=8.6, 1.4 Hz, H-9), 8.48 (1H, br d, J=8.6 Hz, H-6). FAB-MS *m/z*: 204 (MH^+), 206 (MH^++2). *Anal.* Calcd for $C_{11}H_6ClNO$: C, 64.88; H, 2.97; N, 6.88. Found: C, 65.12; H, 3.21; N, 6.99. A later fraction eluted with the same solvent system on chromatography was evaporated and the residue was recrystallized from petroleum ether to give **14a** (48.0 mg, 24%) as pale yellow feathers. The spectroscopic properties were identical to those described for **14a**.

5,7-Dichloro-1,2-dihydrofuro[2,3-*c*]isoquinoline (14b) and 5,7-Dichlorofuro[2,3-*c*]isoquinoline (15b) To a solution of **4b** (1.00 g, 4.53 mmol) in dry $CHCl_3$ (250 ml) was added *n*-amyl nitrite (2.12 g, 18.2 mmol) and the reaction mixture was then refluxed for 0.5 h. After cooling, the solution was evaporated *in vacuo* and the residue was chromatographed on silica gel. An early fraction eluated with petroleum ether–diethyl ether (9 : 1) was evaporated and the residue was recrystallized from ethanol to give **15b** (110 mg, 10%) as pale yellow feathers, mp 174—175 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.21 (1H, d, J=2.3 Hz, H-1), 7.78 (1H, dd, J=8.8, 2.0 Hz, H-8), 7.82 (1H, d, J=2.3 Hz, H-2), 8.09 (1H, d, J=8.8 Hz, H-9), 8.46 (1H, d, J=2.0 Hz, H-6). FAB-MS *m/z*: 238 (MH^+), 240 (MH^++2). *Anal.* Calcd for $C_{11}H_5Cl_2NO$: C, 55.50; H, 2.12; N, 5.88. Found: C, 55.51; H, 2.35; N, 5.83. A later chromatographic fraction eluted with the same solvent system was recrystallized from ethanol to give **14b** (200 mg, 18%) as pale yellow feathers. The spectroscopic properties were identical to those described for **14b**.

1,2-Dihydrofuro[2,3-*c*]isoquinoline (16) To a solution of **14a** (490 mg, 2.38 mmol) in benzene–methanol (1 : 1, 100 ml) were added 10% palladium carbon (1.00 g) and KOH (134 mg, 2.40 mmol) and the mixture was then stirred under an atmosphere of H_2 for 24 h. After filtration of the reaction mixture, the mother liquid was evaporated *in vacuo*. The residue was recrystallized from benzene to give **16** (226 mg, 55%) as colorless prisms, mp 125—127 °C (dec.). ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 3.50 (2H, t, J=9.0 Hz, H-1), 4.73 (2H, t, J=9.0 Hz, H-2), 7.36—7.46 (1H, m, H-7), 7.65—7.72 (2H, m, H-8, 9), 8.04 (1H, br d, J=8.4 Hz, H-6), 8.62 (1H, s, H-5). FAB-MS *m/z*: 172 (MH^+). FAB-HR-MS *m/z*: 172.0794 (Calcd for $C_{11}H_{10}NO$: 172.0762).

Furo[2,3-*c*]isoquinoline (11) Run 1: To a solution of **16** (70.0 mg, 0.409 mmol) in chlorobenzene (25 ml) was added DDQ (280 mg, 1.23 mmol) and the reaction mixture was then refluxed for 1 h. After evaporation of solvent, the residue was chromatographed on silica gel. The eluate of $CHCl_3$ was recrystallized from *n*-hexane to give **11** (64.0 mg, 93%) as colorless prisms, mp 131—132 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.25 (1H, d, J=2.3 Hz, H-1), 7.60 (1H, m, H-7), 7.80 (1H, m, H-8), 7.83 (1H, d, J=2.3 Hz, H-2), 8.08—8.18 (2H, m, H-6, 9), 8.99 (1H, s, H-5). FAB-MS *m/z*: 170 (MH^+). FAB-HR-MS *m/z*: 170.0615 (Calcd for $C_{11}H_8NO$: 170.0606).

Run 2: To a solution of **15a** (68.0 mg, 0.334 mmol) in benzene–methanol (1 : 1, 5.0 ml) were added 10% palladium carbon (100 mg) and KOH (18.0 mg, 0.34 mmol) and the reaction mixture was then stirred under an atmosphere of H_2 for 24 h. After filtration of the reaction mixture, the mother liquid was evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of petroleum ether–diethyl ether (9 : 1) was evaporated and the residue was recrystallized from *n*-hexane to give desired **11** (30.0 mg, 53%) as colorless prisms. The spectroscopic properties were identical to those for **11** described above.

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