Polycyclic *N*-Heterocyclic Compounds. Part 60[1]: Reactions of 3-(2-Cyanophenyl)quinazolin-4(3*H*)-ones with Primary Amines

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The reaction of 3-(2-cyanophenyl)quinazolin-4(3*H*)-one with various primary alkylamines gave 3-alkylquinazolin-4(3*H*)-ones *via* an addition of the nucleophile, ring opening, and ring closure (ANRORC) mechanism. This type of reaction required hydroxy group functionality in either the solvent or reagent. When hydroxylamine was used as nitrogen nucleophile, the intermediate of this reaction was isolated and found to be an amide oxime. When ethylenediamine was used as the nucleophile, the amidine moiety of the intermediate decomposed to give a benzanilide.

Key words nucleophile addition; ring opening; ring closure; 3-alkylquinazolin-4(3*H*)-one; primary amine; heterocycle

3-Substituted-quinazolin-4(3*H*)-ones are prominent structures in the fields of medicinal and natural product chemistry.[2] Their related analogues are, therefore, attractive for potential pharmaceutical applications.

In our previous paper,[1,3] we described that fused 3-(2-bromoethyl)pyrimidin-4(3*H*)-ones (**1**) can react with primary alkylamines to afford abnormal rearranged products (fused 3-alkyl-4-alkyliminopyrimidines (**2**)) in addition to substituted 3-(2-alkylaminoethyl) derivatives (Fig. 1). The abnormal rearranged products seemed to be as a result of a new type of Dimroth rearrangement. We also showed that one of the rearranged products had considerable antidepressant activity, comparable to that of imipramine.

In 2000, W. Szczepankiewicz and J. Suwinski reported the one-pot reaction of 2-aminobenzonitrile and formic acid to form 3-(2-cyanophenyl)quinazolin-4(3*H*)-one (**3**), instead of quinazolin-4(3*H*)-one, which was the anticipated product.[4] We, therefore, wondered if a Dimroth-type rearrangement with primary alkylamines could be applied to substrate **3** to afford 3-alkyl-4-alkyliminoquinazolines. Another possibility was that an addition of the nucleophile, ring opening, and ring closure (ANRORC) reaction could occur to give 3-alkylquinazolin-4(3*H*)-ones (**4**). There have already been shown that N^1-(2,4-dinitrophenyl (or 4-nitrophenyl))inosines with primary alkylamines afford N^1-alkyl inosines *via* an ANRORC mechanism.[5—9] Here we have described the reaction of **3** with primary alkylamines in detail.

First, we tested the reaction of **3** with methylamine in *N*,*N*-dimethylformamide (DMF) at room temperature. The product **4a** in 56% yield was obtained with 2-aminobenzonitrile as a side product, as confirmed by TLC (Chart 1). In the ^{1}H-NMR spectrum of **4a**, one methyl group appeared at 3.61 ppm, one proton singlet of the pyrimidine ring appeared at 8.06 ppm, and four aromatic region signals of the 2-cyanophenyl moiety of **3** disappeared. In the IR spectrum of **4a**, the appearance of a lactam carbonyl band at 1670 cm^{-1} and disappearance of the nitrile band were observed. These results suggested that an ANRORC reaction had occurred in the reaction of **3** with methylamine. Similar results were seen when ethylamine was used to give the product **4b** in 52% yield.

In addition, a reaction between **3** and *n*-propylamine did not proceed at room temperature, as shown by TLC analysis. Contrary to the reactions with methylamine or ethylamine, which were added as methanol or aqueous solutions, respectively, *n*-propylamine was used as a neat in DMF solution; we therefore assumed that a protic solvent was necessary to allow this ANRORC reaction. Addition of methanol as a co-solvent with DMF was tested to give the desired product **4c** in 51% yield. We also tested combining **3** with *tert*-butylamine in the presence of methanol in DMF; however, no reaction occurred. Perhaps, steric hindrance of the *tert*-butyl group prohibited nucleophilic attack of amino functionality to **3**. Furthermore, the reaction of **3** with dimethylamine did not proceed at all. We theorized that if primary alkylamines with hydroxy group functionalities (*i.e.* aminoalcohol) were used in this reaction, a protic co-solvent would not be necessary for this reaction to occur. The reactions of **3** with 2-aminoethanol and 3-aminopropanol in DMF without methanol at elevated temperatures proved that this assumption was true; these reactions produced the products **4d** and

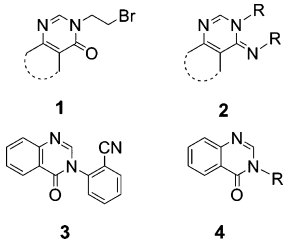

Fig. 1. Substrates (**1** and **3**) with Primary Alkylamines and Their Rearranged Products (**2** and **4**)

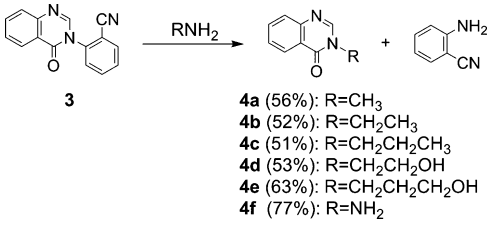

Chart 1. Reaction of **3** with Primary Alkylamines

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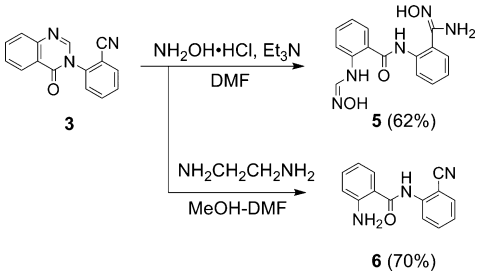

Chart 2. Reaction of **3** with Hydroxylamine and Ethylenediamine

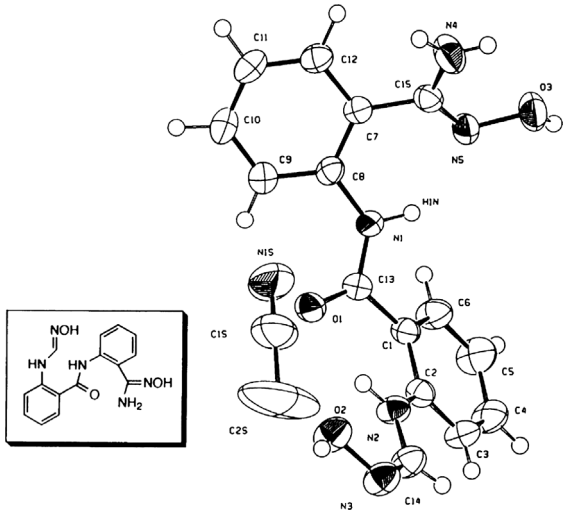

Fig. 2. ORTEP Representation of **5**

4e in 53% and 63% yield, respectively.

Next we turned our attention to using hydrazine or hydroxylamine as nitrogen nucleophiles. When the reaction of **3** was conducted with hydrazine in DMF with methanol as a co-solvent at 80 °C, the product **4f** was obtained in 77% yield. In the case of hydroxylamine, benzanilide derivative **5** (62%), rather than the ANRORC product, was obtained (Chart 2). In the ^{1}H-NMR spectrum of **5**, one proton singlet signal from the 2-H position of **3** disappeared and six protons were exchangeable with D_2O. In the IR spectrum of **5**, disappearance of the nitrile band was observed. These spectroscopic data support a reaction mechanism in which the pyrimidin-4(3*H*)-one ring of **3** was cleaved by nucleophilic attack of hydroxylamine at the C-2 position and the nitrile group was hydroxylaminolyzed to amide oxime. The structure of **5** was confirmed by X-ray crystal structure analysis as shown in Fig. 2. Mass spectrometry spectrum and elemental analysis also confirmed this structure. As far as we know, this type of pyrimidine ring cleavage has not been reported elsewhere.

We then used ethylenediamine as the nitrogen nucleophile. When the reaction of **3** was conducted with ethylenediamine in DMF with methanol as a co-solvent at room temperature, the ring-cleaved benzanilide derivative **6** was obtained in 70% yield. To confirm the structure of **6**, we reduced *N*-(2-cyanophenyl)-2-nitrobenzamide[10] to give **6** along with **7**[11] as a byproduct (Chart 3). All spectroscopic and analytical data of **6** formed by the reduction reaction were identical to those of **6** formed by the ethylenediamine reaction.

Considering that this reaction required hydroxy group

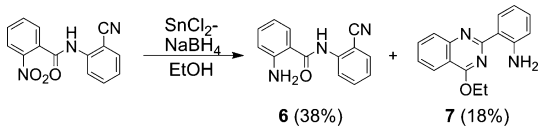

Chart 3. Preparation of **6**

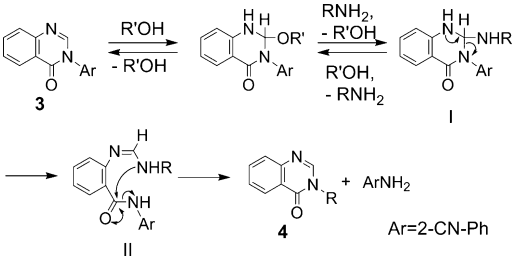

Chart 4. Mechanistic Proposal for Formation of **4**

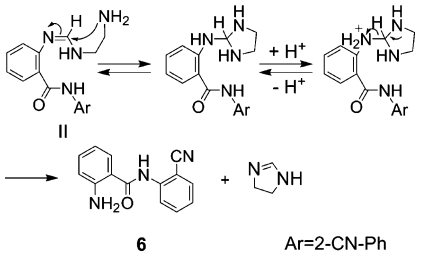

Chart 5. Mechanistic Proposal for Formation of **6**

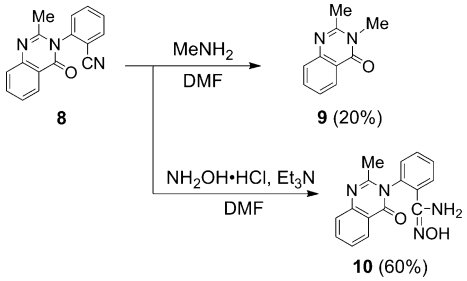

Chart 6. Reaction of **8** with Methylamine and Hydroxylamine

functionality, a possible proposed reaction mechanism of **3** to **4** is shown in Chart 4. First, covalent alcoholation or hydration to the C-2 position of **3** facilitates nucleophilic attack of the amine nucleophile (I). Next, ring cleavage between C-2 and N-3 occurs to give a benzanilide derivative with prototropy (II). The amidine moiety first attacks the amide carbonyl and then replaces 2-aminobenzonitirile to give **4**. In the case of hydroxylamine, the intermediate amide oxime (II) does not have enough nucleophilicity to allow attack of the amide carbonyl moiety. In addition, the 2′-cyano group also reacts with hydroxylamine to give the amide oxime of **5**. In the case of ethylenediamine, intermediate II is rapidly decomposed before cyclization to give **6** *via* a 5-*exo*-trig cyclization (Chart 5).

To support our proposed reaction mechanism, we introduced a methyl group at the C-2 position of **3**. If nucleophilic attack of the amine at the C-2 position is essential for this reaction, a methyl group here would greatly inhibit the reaction. 3-(2-Cyanophenyl)-2-methylquinazolin-4(3*H*)-one (**8**)[12] was allowed to react with methylamine in DMF (Chart 6).

Contrary to the case of **3**, we observed that this reaction did not proceed at room temperature, as judged by TLC analysis. Introduction of the methyl moiety at C-2, therefore, prohibited the reaction from taking place. When the reaction solution was heated to 60 °C, the product **9** was obtained in 20% yield. This rather low yield was due to side products which were indicated by TLC. Finally, we reacted **8** with hydroxylamine. The reaction did not proceed; however, the cyano group at the C-2′ position simply hydroxylaminolyzed to an amide oxime to give **10** in 60% yield. We are currently exploring their structure–activity relationships of the reaction products for further potential pharmaceutics.

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 FAB-mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol was used as the matrix. The IR spectra were recorded on a Japan Spectroscopic FT/IR-200 spectrophotometer with nujol and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 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; quint, quintet; br, broad; m, multiplet. Solvent systems are as follows: methylamine as a 40% methanol solution, ethyl amine as a 70% aqueous solution, and other amines as neat. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). TLC was carried out on Kieselgel 60F254 (Merck).

The structure on X-ray analysis was solved by direct methods with MITHRIL[13] and DIRDIF[14] and refined by the full-matrix least squares method by using TEXSAN.[15] H atoms were found by difference synthesis and refined isotropically. The displacement ellipsoids were drawn with the aid of ORTEP II.[16] Most of the calculations were performed on a VAX 3100 computer using TEXSAN at the X-ray Laboratory of Okayama University.

3-(2-Cyanophenyl)quinazolin-4(3*H*)-one (3) 2-Aminobenzonitrile (3.00 g, 25.4 mmol) was added to formic acid (50 ml) and the solution was stirred at 80 °C for 15 h. After cooled to room temperature, water (50 ml) was added, and then allowed to stand for 3 h. The precipitate was filtered and the solid was recrystallized from DMF-methanol to give **3** (1.80 g, 57%) as colorless prisms. mp 192—193 °C (lit.[4] 196—197 °C). ^{1}H-NMR (DMSO-d_6) δ: 7.61—8.28 (8H, m, Ar-H), 8.46 (1H, s, H-2). IR (nujol) cm^{-1}: 2238 (CN), 1685 (CO). FAB-MS *m*/*z*: 248 (MH^+). *Anal.* Calcd for $C_{15}H_9N_3O$: C, 72.87; H, 3.67; N, 16.99. Found: C, 73.16; H, 3.74; N, 16.99.

General Procedure for the Reaction of 3 with Primary Amines To a solution of **3** (300 mg, 1.21 mmol) was added primary amine (12.1 mmol) and the solution was stirred for the appropriate time. Water (50 ml) was added and extracted with ethyl acetate (50 ml×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in vacuo. The residue was purified by column chromatography and/or recrystallization.

3-Methylquinazolin-4(3*H*)-one (4a) Reaction time was 10 h in DMF (20 ml) at room temperature. The residue was chromatographed on silica gel. Eluate of ethyl acetate–*n*-hexane (1 : 5, v/v) was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **4a** (109 mg, 56%) as colorless needles. mp 103—105 °C (lit.[17] 106 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.61 (3H, s, $-CH_3$), 7.47—7.82 (3H, m, H-6, 7, and 8), 8.06 (1H, s, H-2), 8.32 (1H, dd, J=7.4, 1.4 Hz, H-5). IR (nujol) cm^{-1}: 1670 (CO). FAB-MS *m*/*z*: 161 (MH^+). *Anal.* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.28; H, 5.05; N, 17.60.

3-Ethylquinazolin-4(3*H*)-one (4b) Reaction time was 10 h in DMF (20 ml) at room temperature. The residue was chromatographed on silica gel. Eluate of ethyl acetate–*n*-hexane (1 : 5, v/v) was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **4b** (109 mg, 52%) as colorless needles. mp 99—101 °C (lit.[18] 76.5—78.5 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.2 Hz, $-CH_3$), 4.08 (2H, q, J=7.2 Hz, $-CH_2-$), 7.46—7.82 (3H, m, H-6, 7 and 8), 8.06 (1H, s, H-2), 8.32 (1H, dd, J=7.5, 1.4 Hz, H-5). IR (nujol) cm^{-1}: 1677 (CO). FAB-MS *m*/*z*: 175 (MH^+). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.94; H, 5.66; N, 16.11.

3-*n*-Propylquinazolin-4(3*H*)-one (4c) Reaction time was 10 h in DMF (20 ml) and methanol (2 ml) at room temperature. The residue was chromatographed on silica gel. Eluate of ethyl acetate–*n*-hexane (1 : 6, v/v) was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **4c** (116 mg, 51%) as colorless needles. mp 82—84 °C (lit.[18] 82—83 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.4 Hz, $-CH_3$), 1.84 (2H, quint, J=7.4 Hz, $-C\underline{H}_2CH_3$), 3.98 (2H, t, J=7.4 Hz, $-NC\underline{H}_2CH_2-$), 7.46—7.82 (3H, m, H-6, 7, and 8), 8.04 (1H, s, H-2), 8.32 (1H, dd, J=7.8, 1.4 Hz, H-5). IR (nujol) cm^{-1}: 1677 (CO). FAB-MS *m*/*z*: 189 (MH^+). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.94; H, 6.27; N, 15.01.

3-(2-Hydroxyethyl)quinazolin-4(3*H*)-one (4d) Reaction time was 6 h in DMF (20 ml) at 90 °C. The residue was recrystallized from ethyl acetate to give **4d** (122 mg, 53%) as colorless needles. mp 152—153 °C (lit.[19] 150—152 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.28 (1H, br s, D_2O exchangeable, OH), 4.01 (2H, t, J=4.9 Hz, $C\underline{H}_2OH$), 4.16 (2H, t, J=4.9 Hz, NCH_2), 7.43 (1H, td, J=7.6, 1.5 Hz, H-6), 7.59 (1H, dd, J=7.6, 1.5 Hz, H-8), 7.72 (1H, td, J=7.6, 1.4 Hz, H-7), 8.07 (1H, s, H-2), 8.15 (1H, dd, J=7.8, 1.4 Hz, H-5). IR (nujol) cm^{-1}: 3255 (OH), 1675 (CO). FAB-MS *m*/*z*: 191 (MH^+). *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.06; H, 5.26; N, 14.82.

3-(3-Hydroxypropyl)quinazolin-4(3*H*)-one (4e) Reaction time was 2 d in DMF (20 ml) at 60 °C. The residue was recrystallized from ethyl acetate–*n*-hexane to give **4e** (156 mg, 63%) as colorless needles. mp 102—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.97—2.12 (2H, m, $CH_2C\underline{H}_2CH_2$), 3.02 (1H, br s, D_2O exchangeable, OH), 3.64 (2H, t, J=6.2 Hz, $C\underline{H}_2OH$), 4.22 (2H, t, J=6.2 Hz, NCH_2), 7.49—7.85 (3H, m, H-6, 7, and 8), 8.10 (1H, s, H-2), 8.32 (1H, dd, J=7.5, 1.4 Hz, H-5). IR (nujol) cm^{-1}: 3280 (OH), 1670 (CO). FAB-MS *m*/*z*: 205 (MH^+). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.64; H, 6.19; N, 13.54.

3-Aminoquinazolin-4(3*H*)-one (4f) To a solution of **3** (300 mg, 1.21 mmol) in DMF (20 ml) and methanol (2 ml) was added hydrazine dihydrochloride (1.27 g, 12.1 mmol) and triethylamine (1.23 g, 12.2 mmol) then the solution was stirred at 80 °C for 1.5 d. After evaporation of solvent (about 10 ml), water (50 ml) was added, and then allowed to stand in refrigerator overnight. The precipitate was filtered and the solid was recrystallized from ethyl acetate to give **4f** (150 mg, 77%) as dark yellow needles. mp 203—204 °C (lit.[20] 209—212 °C). ^{1}H-NMR (DMSO-d_6) δ: 5.89 (2H, br s, D_2O exchangeable, NH_2), 7.40—8.32 (4H, m, Ar-H), 8.38 (1H, s, H-2). IR (nujol) cm^{-1}: 3290, 3160 (NH), 1685 (CO). FAB-MS *m*/*z*: 162 (MH^+). *Anal.* Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.59; H, 4.46; N, 26.37.

***N*-(2-(*N*′-Hydroxycarbamimidoyl)phenyl)-2-(*N*′-hydroxyformimidamido)benzamide (5)** To a solution of **3** (1.70 g, 6.88 mmol) in DMF (20 ml) was added hydroxylamine hydrochloride (2.39 g, 34.4 mmol) and triethylamine (3.06 g, 30.2 mmol) then the mixture was stirred at room temperature for 15 h. Water (50 ml) was added and then allowed to stand for 1 h. The precipitate was filtered and the solid was recrystallized from ethyl acetate to give **5** (1.34 g, 62%) as colorless prisms. mp 160—164 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 6.28 (2H, br s, D_2O exchangeable, NH_2), 7.00—7.10 (1H, m, Ar-H), 7.19 (1H, br t, J=7.5 Hz, Ar-H), 7.37—7.57 (3H, m, Ar-H), 7.51—7.84 (2H, m, Ar-H), 7.77 (1H, d, changed to s after addition of D_2O, J=10.5 Hz, $C\underline{H}$=NOH), 8.56 (1H, br d, J=7.8 Hz, Ar-H), 10.17 (1H, s, D_2O exchangeable, NH or OH), 10.18 (1H, s, D_2O exchangeable, NH or OH), 10.75 (1H, br d, J=10.5 Hz, D_2O exchangeable, $N\underline{H}$–CH=NOH), 12.33 (1H, br s, D_2O exchangeable, NH or OH). IR (nujol) cm^{-1}: 3455, 3340, 3170 (NH and OH), 1635 (CO). FAB-MS *m*/*z*: 314 (MH^+). *Anal.* Calcd for $C_{15}H_{15}N_5O_3 \cdot 1/2\ H_2O$: C, 55.90; H, 5.00; N, 21.73. Found: C, 55.69; H, 4.73; N, 21.87.

The crystals were grown from an acetonitrile solution by slow evaporation. This analytical sample was dried around 100 °C under vacuum.

Crystal Structure Analysis of 5[21] Crystal data: $C_{15}H_{15}N_5O_3 \cdot 0.5C_2H_3N$; M_r=333.63; monoclinic, space group $C2/c$ (#15), a=11.731(6), b=14.589(8), c=20.04(1) Å, β=104.66(4)°, V=3319(1) Å^3; Z=8; D_c=1.370 g cm^{-3}. A crystal of size 0.430×0.300×0.500 mm was examined by using graphite-monochromated Mo$K\alpha$ radiation (λ=0.71073 Å). Cell dimensions were obtained from 25 reflections ($19.0<2\theta<22.0°$). In total 4010 reflections were measured by the ω–2θ scan method, and 3812 of these were unique (R_{int}=0.063). Refinements were carried out including all the hydrogen atoms except those of the methyl group of the solvent molecule by using 2859 reflections with $I>2.00\ \sigma(I)$ within $2\theta_{max}$ of 55°. R=0.050, R_w=0.052, S=1.73. The formular unit was confirmed by the structure analysis. The solvent molecule lies on the two-fold axis in the unit cell.

2-Amino-*N*-(2-cyanophenyl)benzamide (6) To a solution of **3** (300 mg, 1.21 mmol) in DMF (20 ml) and methanol (2 ml) was added ethylenediamine (730 mg, 12.1 mmol) and the solution was stirred at room temperature for 1.5 d. Water (50 ml) was added and then allowed to stand for 1 h.

The precipitate was filtered and the solid was recrystallized from ethyl acetate–*n*-hexane to give **6** (201 mg, 70%) as colorless needles. mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.61 (2H, br s, D_2O exchangeable, NH_2), 6.70—6.83 (2H, m, Ar-H), 7.15—7.37 (2H, m, Ar-H), 7.54—7.71 (3H, m, Ar-H), 8.37 (1H, br s, D_2O exchangable, CONH), 8.50 (1H, dd, J=8.7, 1.3 Hz, Ar-H). IR (nujol) cm^{-1}: 3465, 3370, 3300, 3250 (NH), 2225 (CN), 1650 (CO). FAB-MS *m*/*z*: 238 (MH^+). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.83; H, 4.75; N, 17.88.

Alternative Preparation of 2-Amino-*N*-(2-cyanophenyl)benzamide (6) with 2-(2-Aminophenyl)-4-ethoxyquinazoline (7) To a hot mixture of *N*-(2-cyanophenyl)-2-nitrobenzamide[10] (1.00 g, 3.74 mmol) and $SnCl_2$ dihydrate (4.22 g, 18.7 mmol) in ethanol (50 ml) at 60 °C was added $NaBH_4$ (71.0 mg, 1.88 mmol) and the mixture was refluxed for 1 h. The reaction mixture was poured onto ice water (100 ml), and then neutralized by 10% aq. NaOH. After evaporation *in vacuo*, water (100 ml) was added and then extracted with ethyl acetate (100 ml×3). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, and then evaporated *in vacuo*. The residue was chromatographed on silica gel. Eluate of ethyl acetate–*n*-hexane (1 : 5, v/v) was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **7** (180 mg, 18%) as yellow needles. Further eluate of ethyl acetate–*n*-hexane (1 : 5, v/v) was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **6** (340 mg, 38%) as colorless needles. **7**: mp 87 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (3H, t, J=7.1 Hz, –CH_3), 4.74 (2H, q, J=7.1 Hz, –CH_2–), 6.68 (2H, br s, D_2O exchangeable, NH_2), 6.78 (2H, br t, J=7.5 Hz, Ar-H), 7.18—7.30 (1H, m, Ar-H), 7.42—7.53 (1H, m, Ar-H), 7.71—7.92 (2H, m, Ar-H), 8.14 (1H, br d, J=7.9 Hz, Ar-H), 8.57 (1H, br d, J=7.5 Hz, Ar-H). IR (nujol) cm^{-1}: 3400, 3270 (NH). FAB-MS *m*/*z*: 266 (MH^+). *Anal.* Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.48; H, 5.66; N, 16.04.

3-(2-Cyanophenyl)-2-methylquinazolin-4(3*H*)-one (8) To a mixture of 2-acetylaminobenzoic acid (10.0 g, 55.8 mmol) and 2-aminobenzonitrile (6.60 g, 55.9 mmol) was added $POCl_3$ (50 ml) and the mixture was stirred at 60—70 °C for 1.5 h. After cooled to room temperature, the reaction mixture was poured onto ice water (50 ml), neutralized with $NaHCO_3$, and then extracted with ethyl acetate (100 ml×3). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from DMF-methanol to give **8** (4.37 g, 30%) as pale yellow plates. mp 162—163 °C (lit.[12] 165—166 °C). ^{1}H-NMR (DMSO-d_6) δ: 2.17 (3H, s, –CH_3), 7.54—8.17 (8H, m, Ar-H). IR (nujol) cm^{-1}: 2230 (CN), 1685 (CO). FAB-MS *m*/*z*: 262 (MH^+). *Anal.* Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.55; H, 4.24; N, 16.06.

2,3-Dimethylquinazolin-4(3*H*)-one (9) To a solution of **8** (300 mg, 1.15 mmol) in DMF (20 ml) was added methylamine (891 mg, 11.5 mmol) and the solution was stirred at 60 °C for 3 d in a sealed tube. Water (50 ml) was added, and then extracted with ethyl acetate (50 ml×3). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, and then evaporated *in vacuo*. The residue was chromatographed on silica gel. Eluate of ethyl acetate–*n*-hexane (1 : 2, v/v) was evaporated and the residue was recrystallized from ethyl acetate–*n*-hexane to give **9** (40.0 mg, 20%) as colorless needles. mp 108—109 °C (lit.[22] 104—107 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s, –CH_3), 3.64 (3H, s, –CH_3), 7.44 (1H, br t, J=7.0 Hz, H-6), 7.61 (1H, br d, J=7.0 Hz, H-8), 7.68—7.79 (1H, m, H-7), 8.32 (1H, dd, J=8.0, 1.6 Hz, H-5). IR (nujol) cm^{-1}: 1670 (CO). FAB-MS *m*/*z*: 175 (MH^+). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.58; H, 6.17; N, 15.80.

2-(3,4-Dihydro-2-methyl-4-oxoquinazolin-3-yl)benzamide Oxime (10) To a solution of **8** (500 mg, 1.91 mmol) in DMF (40 ml) were added hydroxylamine hydrochloride (666 mg, 9.58 mmol) and triethylamine (970 mg, 9.59 mmol), and the mixture was stirred at room temperature for 15 h. Water (50 ml) was added, and then allowed to stand for 1 h. The precipitate was filtrated and the solid was recrystallized from DMF-methanol to give **10** (338 mg, 60%) as colorless needles. mp 253—255 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.14 (3H, s, –CH_3), 5.60 (2H, br s, D_2O exchangeable, NH_2), 7.34—7.86 (7H, m, Ar-H), 8.07 (1H, br d, J=8.0 Hz, H-5), 9.39 (1H, s, D_2O exchangeable, OH). IR (nujol) cm^{-1}: 3455, 3357, 3170 (NH and OH), 1670 (CO). FAB-MS *m*/*z*: 295 (MH^+). *Anal.* Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.15; H, 4.64; N, 19.11.

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References and Notes

1) Part 59: Okuda K., Ohtomo H., Tanaka F., Hirota T., Sasaki K., *Chem. Pharm. Bull.*, **57**, 755—758 (2009).
2) Michael J. P., *Nat. Prod. Rep.*, **24**, 223—246 (2007).
3) Ohtomo H., Tagata T., Sasaki K., Hirota T., Okuda K., *Tetrahedron*, **63**, 12541—12546 (2007).
4) Szczepankiewicz W., Suwinski J., *Chem. Heterocycl. Compd.* (New York), **36**, 809—810 (2000).
5) Oliviero G., Amato J., Borbone N., D'Errico S., Piccialli G., Bucci E., Piccialli V., Mayol L., *Tetrahedron*, **64**, 6475—6481 (2008).
6) Oliviero G., Amato J., Borbone N., D'Errico S., Piccialli G., Mayol L., *Tetrahedron Lett.*, **48**, 397—400 (2007).
7) Oliviero G., Amato J., D'Errico S., Borbone N., Piccialli G., Mayol L., *Nucleosides, Nucleotides Nucleic Acids*, **26**, 1649—1652 (2007).
8) Narukulla R., Shuker D. E. G., Xu Y.-Z., *Nucleic Acids Res.*, **33**, 1767—1778 (2005).
9) Napoli L. D., Messere A., Montesarchio D., Piccialli G., *J. Org. Chem.*, **60**, 2251—2253 (1995).
10) de Mayo P., Ryan J. J., *Can. J. Chem.*, **45**, 2177—2190 (1967).
11) $SnCl_2$ acts as a Lewis acid to activate the nitrile group. $SnCl_2$ facilitates nucleophilic attack of ethanol to give imino ester, which then cyclizes to give a quinazoline structure. For base-catalyzed quinazoline formation see: Breukink K. W., Krol L. H., Verkade P. E., Wepster B. M., *Recl. Trav. Chim., Pays-Bas*, **76**, 401—414 (1957).
12) Harrison D. R., Kennewell P. D., Taylor J. B., *J. Heterocycl. Chem.*, **14**, 1191—1196 (1977).
13) Gilmore C. J., *J. Appl. Cryst.*, **17**, 42—46 (1984).
14) Beurskens P. T., "DIRDIF. Direct Methods for Difference Structures—an Automatic Procedure for Phase Extension and Refinement of Difference Structure Factors," Technical Report Vol. 1, Crystallography Laboratory, Toernooiveld, 6525 ED Nijmegen, The Netherlands, 1984.
15) Molecular Structure Corporation, 1985.
16) Johnson C. K., *ORTEP II*, 1976.
17) Santagati N. A., Bousquet E., Spadaro A., Ronsisvalle G., *Il Farmaco*, **54**, 780—784 (1999).
18) Ouyang G., Zhang P., Xu G., Song B., Yang S., Jin L., Xue W., Hu D., Lu P., Chen Z., *Molecules*, **11**, 383—392 (2006).
19) Reisch J., Gunaherath G. M. K. B., *J. Nat. Prod.*, **52**, 404—407 (1989).
20) Plescia S., Bajardi M. L., Raffa D., Daidone G., Matera M., Caruso A., Amico-Roxas M., *Eur. J. Med. Chem.*, **21**, 291—295 (1986).
21) Crystallographic data for the structure of **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 733445. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
22) Takeuchi H., Hagiwara S., Eguchi S., *Tetrahedron*, **45**, 6375—6386 (1989).