Polycyclic N-Heterocyclic Compounds. Part 601: Reactions of 3-(2-Cyanophenyl)quinazolin-4(3H)-ones with Primary Amines

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The reaction of 3-(2-cyanophenyl)quinazolin-4(3H)-one with various primary alkylamines gave 3-alkylquinazolin-4(3H)-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 amide moiety of the intermediate decomposed to give a benzaldehyde.

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

3-Substituted-quinazolin-4(3H)-ones are prominent structures in the fields of medicinal and natural product chemistry. 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(3H)-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. Swiniński reported the one-pot reaction of 2-aminobenzonitrile and formic acid to give a benzanilide.4) When ethylenediamine was used as the nucleophile, the amidine moiety of the intermediate decomposed to give a lactam. When tert-butylamine was used as a nucleophile, the intermediate decomposed to give a benzaldehyde.

Contrary to the reactions with methylamine or ethylamine, tert-butylamine was used as a neat in DMF solution; 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 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 Alkamines and Their Rearranged Products (2 and 4)](image-url)
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 1H-NMR spectrum of 5, one proton singlet signal from the 2-H position of 3 disappeared and six protons were exchangeable with D2O. 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(3H)-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\(^\text{10}\) to give 6 along with 7\(^\text{11}\) 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 functionality, a possible proposed reaction mechanism of 3 to 4 is shown in Chart 4. First, covalent alcoholation or hydrazination 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-aminobenzonitrile 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 \(2^\text{1032}\)-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(3H)-one (8)\(^\text{12}\) was allowed to react with methyamine 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 pharmacueticals.

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 Japon Spectroscopic FT/IR-200 spectrophotometer with nujol and frequencies are expressed in cm⁻¹. The ¹H-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: methylene as a 40% methanol solution, ethyl amine as a 70% aqueous solution. 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 Japon Spectroscopic FT/IR-200 spectrophotometer with nujol and frequencies are expressed in cm⁻¹. The ¹H-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: methylene as a 40% methanol solution, ethyl amine as a 70% aqueous solution.

Crystal Structure Analysis of 5
Crystal Structure of 5 (C₂₀H₁₆N₄O₄). To a solution of 3 (300 mg, 1.21 mmol) in DMF (20 ml) and methanol (2 ml) was added hydrazine hydrate (1.27 g, 21.1 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 6 (150 mg, 75%) as yellow needle crystals.

Crystal Structure Analysis of 4
Crystal Structure of 4 (C₁₀H₈N₂O₂). To a solution of 3 (300 mg, 1.21 mmol) in DMF (20 ml) and methanol (2 ml) was added hydrazine hydrate (1.27 g, 21.1 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 6 (150 mg, 75%) as yellow needle crystals.

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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 (6) and the residue was recrystallized from ethyl acetate–hexane to give 8 (20 mg, 70%) as colorless needles. mp 162—163 °C. 1H-NMR (CDCl3) δ: 2.14 (H, s, –CH3), 5.60 (2H, brs, D2O exchangeable, NH2), 7.56 (2H, brs, D2O exchangeable, NH2), 7.34—7.40 (1H, br, J = 7.9 Hz, Ar-H), 8.57 (1H, br, J = 7.5 Hz, Ar-H), 8.57 (1H, brd, J ∼ 7.5 Hz, Ar-H). IR (nujol) cm⁻¹: 3455, 3375, 3170 (NH and OH), 1670 (CO). FAB-MS m/z: 295 (MH⁺). Anal. Calcd for C16H11N3O: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.55; H, 4.24; N, 16.04.

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References and Notes
11) SnCl₂ acts as a Lewis acid to activate the nitrile group. SnCl₂ facilitates nitrileophobic attack of ethanol to give imino ether, 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., React. Chim., Pays-Bas, 76, 401—414 (1975).
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].