Reactions of Anthranilamide with Isocyanates: A New Facile Synthesis of 2,3-Dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one and 3,4-Dihydro-2*H*,6*H*-[1,3]oxazino[2,3-*b*]quinazolin-6-one [1]

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2,3-Dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one **5a** was synthesized from anthranilamide **1** and 2-chloroethyl isocyanate either by a direct reflux in methanol, or by stirring at room temperature in acetonitrile leading to the intermediate, 2-(2-chloroethyl ureido)benzamide **6a** which was subsequently cyclized on heating with an organic base. However, when compound **6a** was refluxed with concentrated hydrochloric acid, it furnished 3-(2-chloroethyl)-2,4-dioxo-1*H*,3*H*-quinazoline **2a** in good yields. 3,4-Dihydro-2*H*,6*H*-[1,3]-oxazino[2,3-*b*]quinazolin-6-one **5b**, 3-(3-chloropropyl)-2,4-dioxo-1*H*,3*H*-quinazoline **2b** and 2-(3-chloropropyl ureido)benzamide **6b** were obtained similarly from **1** and 3-chloropropyl isocyanate.

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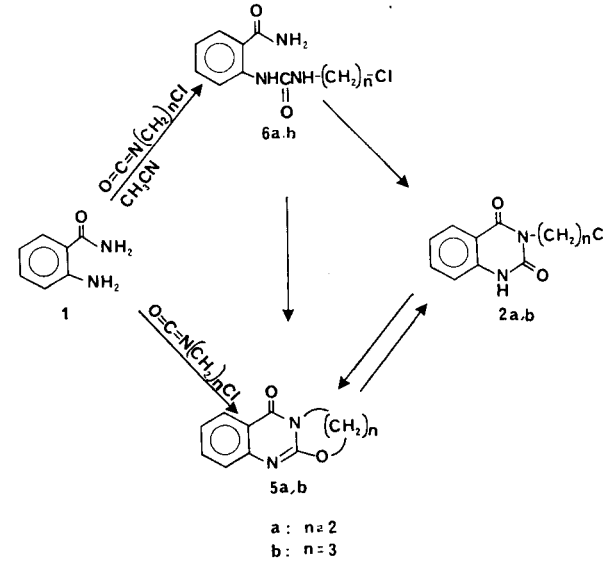
In a previous paper, we reported a convenient synthesis of 3-substituted 2-mercapto-1*H*,3*H*-quinazolin-4-ones by treating anthranilamide **1** with alkyl or aryl isothiocyanates [2]. In a continuous study, we became interested in improving the synthesis of 3-(2-chloroethyl)-2,4-dioxo-1*H*,3*H*-quinazoline **2a** [3] and 3-(3-chloropropyl)-2,4-dioxo-1*H*,3*H*-quinazoline **2b** [4] which are key intermediates for the synthesis of 3-(2-substituted ethyl)-2,4-dioxo-1*H*,3*H*-quinazolines or 3-(3-substituted propyl)-2,4-dioxo-1*H*,3*H*-quinazoline [5], a clinically useful antihypertensive pharmacophore, such as ketaserine **3**.

There are two methods available in [6] the literature for the synthesis of compound **2a** either through chlorination of 3-(2-hydroxyethyl)-2,4-dioxo-1*H*,3*H*-quinazoline **4** [7] or *via* treatment of 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one **5a** with concentrated hydrochloric acid [8]. Similarly, **2b** has also been analogously synthesized from **5b** by Papadopoulos [4]. Compound **5a** has been previously prepared by Grout and Partridge [7] either from 2,4-dioxo-1*H*,3*H*-quinazoline **7** and 1,2-dibromoethane and/or 2-chloro-3*H*-quinazolin-4-one **8** and ethylene oxide under the influence of alkaline. Another route for the synthesis of compound **5a** *via* iodide-catalyzed ring expansion of 2-[(1-aziridinyl-carbonyl)amino]benzoic acid methyl ester **9** has also been documented [9]. However, to our best knowledge, a convenient synthesis of compound **5a** by a treatment of anthranilamide with 2-chloroethyl isocyanate has not been reported.

At the outset, we reasoned that compound **2a** could be easily obtained by treatment of anthranilamide with 2-chloroethyl isocyanate on the basis of our previously published methods [2,10]. However, when the reaction was performed in acetonitrile by stirring at room temperature, a turbid solution was immediately formed. The only single product isolated from the reaction mixture was shown to be 2-(2-chlorethyl)ureidobenzamide **6a** instead of the desired bicyclic compound **2a**. The attempted conversion of compound **6a** to **2a** was performed by treating with *N*,*N*-diisopropylethylamine in methanol at refluxing temperature. It afforded tricyclic compound **5a** in a good yield rather than the bicyclic compound **2a**.

The failure of further ring closure from compound **6a** to bicyclic or tricyclic compounds in a reaction of anthranilamide and 2-chloroethyl isocyanate was probably due to the poor solubility of compound **6a** in acetonitrile. Thus, under similar condition, when the reaction was carried out in methanol at room temperature, compound **5a** and compound **6a** were formed in the reaction mixture. However, the reaction never proceeded completely and no bicyclic compound **2a** could be observed.



It should be noted that when anthranilamide and 2-chloroethyl isocyanate were refluxed in methanol, the reaction was complete in 24 hours and the tricyclic compound **5a** was isolated as the only product. A reasonable mechanism for this transformation might involve the initial formation of compound **6a** between anthranilamide and 2-chloroethyl isocyanate *via* a nucleophilic addition of the amino group of anthranilamide to the electron deficient carbon of the isocyanato of 2-chlorethyl isocyanate, followed subsequently by a nucleophilic addition of the ureido nitrogen to the carbonyl group of carboxamide resulting in an elimination of ammonia. The released ammonia then immediately catalyzed the ring closure of compound **6a** by enhancing the nucleophilicity of oxygen at the second position.

On the basis of the proposed mechanism, the basic ammonia released from the intermediate promoted a further ring closure of compound **2a** to **5a**. Thus, we assumed that the ring closure of compound **6a** in an acidic medium should result in the formation of bicyclic compound **2a** instead of tricyclic compound **5a**. Therefore, when compound **6a** was refluxed in concentrated hydrochloric acid, it led to the formation of compound **2a** in good yield.

In an attempt to study the scope of this reaction, anthranilamide was similarly reacted with 3-chloropropyl isocyanate. It gave 2-(3-chloropropylureido)benzamide **6b** in 89% yield. The cyclization of **6b** was carried out by refluxing in aqueous ethanol under the catalysis of alkali afford **5b** in 84% yield. In the same manner, compound **2b** was also obtained in a good yield by treating compound **6b** with concentrated hydrochloric acid.

This facile procedure provided a new route towards the synthesis of tricyclic heterocycles or compound **2** and additional studies in this area are in progress.

EXPERIMENTAL

Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. The ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a JOEL FX-100 spectrometer from National Taiwan Normal University Taipei, using DMSO-d_6 as solvent and as internal standard. Mass spectra were obtained on a JOEL Model JMS-D300 GC/MS spectrometer from National Taiwan Normal University. Elemental analysis was carried out on Heraeus Elemental Analyzer in Cheng-Kung University, Tainan.

2-(2-Chloroethyl ureido)benzamide **6a**.

To a mixture of anthranilamide (1.36 g, 10 mmoles) and acetonitrile (30 ml) was added 2-chloroethyl isocyanate (2.11 g, 20 mmoles) over a period of 30 minutes. The mixture was stirred at room temperature for 2 hours. The solid was then collected by filtration and recrystallized from methanol to give 2.27 g (94%) of compound **6a**, mp 167-168°; ^1H nmr (100 MHz, DMSO-d_6): 3.48 (t, 2H, CH_2), 3.72 (t, 2H, CH_2), 7.02 (t, 1H), 7.37-7.54 (m, 4H), 7.7-7.9 (m, 2H), 10.52 (s, 1H); ^{13}C nmr (25 MHz, DMSO-d_6): 41.44, 43.72, 118.81, 119.44, 119.88, 128.05, 131.36, 140.84, 154.51, 170.55; ms: m/z 241 (M^+); ir (potassium bromide): 3363, 3296, 3181, 1664, 1625, 1582, 1553, 1450, 1390, 1301, 1254, 1129, 980, 950, 873, 812, 751 cm^{-1}.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_2$: C, 49.69; H, 5.04; N, 17.38. Found: C, 49.71; H, 5.00; N, 17.45.

3-(2-Chloroethyl)-2,4-dioxo-1*H*,3*H*-quinazoline **2a**.

To a mixture of compound **6a** (10.27 g, 42.5 mmoles) in ethanol (50 ml) was added concentrated hydrochloric acid (30 ml). The mixture was refluxed in an oil bath for 30 minutes. After the mixture was cooled to room temperature, the white precipitated solid was collected by filtration and then recrystallized from ethanol to furnish 7.31 g (77%) of compound **2a**, mp 193-195° (lit [7] mp 195.5-196°); ^1H nmr (100 MHz, DMSO-d_6): 3.8 (t, 2H, CH_2), 4.2 (t, 2H, CH_2), 6.7-7.7 (m, 4H, Ar-H), 11.5 (brs, 1H, NH); ^{13}C nmr (25 MHz, DMSO-d_6): 36, 40, 112, 113, 121, 126, 133, 138, 148, 160; ir (potassium bromide): 3073, 1711, 1643 cm^{-1}.

2,3-Dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one **5a**.

From Compound **6a**.

A mixture of compound **6a** (2.41 g, 10 mmoles) and *N*,*N*-diisopropylethylamine (20 ml) in methanol (20 ml) was refluxed for 24 hours. The solvent was then removed *in vacuo* (60°). The oil residue was dissolved in a small amount of acetonitrile. Water (50 ml) was added to this solution to afford white solid, which was collected by filtration and recrystallized from methanol to give 1.58 g (85%) of compound **5a**, mp 162-163° (lit [7] mp 165°); ^1H nmr (100 MHz, DMSO-d_6): 3.29 (t, 2H, CH_2), 4.71 (t, 2H, CH_2), 7.14-8.1 (m, 4H, Ar-H); ^{13}C nmr (25 MHz, DMSO-d_6): 159.81, 155.81, 148.82, 134.23, 125.72, 125.47, 123.92, 118.08, 66.29, 42.16; ms: m/z 188 (M^+); ir (potassium bromide): 2921, 1688, 1640, 1608, 1559, 1475, 1413, 1337, 1263, 1130, 1018, 982, 917, 866, 772, 738, 694 cm^{-1}.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.79; H, 4.49; N, 14.61.

From Anthranilamide **1**.

To a solution of anthranilamide (3.0 g, 22 mmoles) in methanol (40 ml) was added 2-chloroethyl isocyanate (3.5 g, 33 mmoles). The white solid was formed immediately and the mixture turned into a solution on heating in an oil bath. The resulting suspension was allowed to reflux for 24 hour. After cooling ether (100 ml) was added to the solution to get 3.4 g (82%) of compound **5a**.

2-(3-Chloropropyl ureido)benzamide **6b**.

To a mixture of anthranilamide (1.5 g, 11 mmoles) and acetonitrile (40 ml) was added 3-chloropropyl isocyanate (1.97 g, 17 mmoles) over a 30 minute period. The precipitate was formed immediately and the mixture was stirred at room temperature for 2 days. The solid was then collected by filtration and recrystallized from methanol to give 2.4 g (89%) of compound **6b**, mp 172-173°; ^1H nmr (100 MHz, DMSO-d_6): 1.86 (m, 2H, CH_2), 3.18 (m, 2H, CH_2), 3.66 (t, 2H, CH_2), 6.72-8.28 (m, 7H, Ar-H + NH_2 + NH), 10.27 (s, 1H, NH); ^{13}C nmr (25 MHz, DMSO-d_6): 32.58, 36.72, 43.09, 118.62, 119.39, 119.74, 128.10, 131.40, 141.08, 154.70, 170.65; ir (potassium bromide): 3372, 3271, 3093, 2968, 2942, 1952, 1658, 1619, 1580, 1502, 1444, 1396, 1287, 1229, 1163, 1109, 1048, 983, 949, 879, 802 cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}ClN_3O_2$ (255.75): C, 51.66; H, 5.51; N, 16.43. Found: C, 51.70; H, 5.49; N, 16.42.

3-(3-chloropropyl)-2,4-dioxo-1*H*,3*H*-quinazoline **2b**.

Method A.

A mixture of **6b** (1.05 g, 4 mmoles) and potassium carbonate (0.29 g, 2 mmoles) in methanol (20 ml) was heated under reflux for 24 hours. After cooling to room temperature, the reaction mixture was set free from solvent by evaporating *in vacuo*. The residue was treated with water (50 ml) and adjusted to *p*H 5 with acetic acid. The solid was collected by filtration and recrystallized from methanol to give 0.53 g (56%) of compound **2b**, mp 167-170° (lit [4] mp 168-172°); ^1H nmr (100 MHz, DMSO-d_6): 2.01 (m, 2H, CH_2), 3.66 (t, 2H, CH_2), 3.99 (t, 2H, CH_2), 7.02-7.98 (m, 4H, Ar-H), 11.34 (s, 1H, NH); ^{13}C nmr (25 MHz, DMSO-d_6): 30.64, 43.23 113.65, 114.92, 122.26, 127.17, 134.71, 139.23, 149.93, 161.75, 166.08; ms: m/z 238 (M^+), 204, 203, 189, 176, 146, 119, 92; ir (potassium bromide): 3239,

3195, 1724, 1631, 1491, 1444, 1272, 1117, 1030, 799, 761, 721, 692 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$ (238.75): C, 55.34; H, 4.64; N, 11.73. Found: C, 55.62; H, 4.61; N, 11.59.

Method B.

To a mixture of compound **6b** (1.05 g, 4 mmoles) and ethanol (10 ml) was added concentrated hydrochloric acid (10 ml). The mixture was refluxed in an oil bath for 30 minutes. After the mixture was cooled to room temperature, the white solid was collected by filtration and recrystallized from ethanol to give 0.73 g (75%) of compound **2b**.

3,4-Dihydro-2*H*,6*H*-[1,3]oxazino[2,3-*b*]quinazolin-6-one **5b**.

A mixture of compound **6b** (1.05 g, 4 mmoles), in ethanol (10 ml) and 10% potassium bicarbonate (10 ml) was refluxed in an oil bath for 1 hour. The solvent was evaporated to dryness. To the solid residue was added water (30 ml) and the mixture was neutralized with acetic acid. The resulting needle solid was collected by filtration to give 0.61 g (77%) of compound **5b**, mp 90-91° (lit [4] 124-128°); ^1H nmr (DMSO-d_6): 2.22 (m, 2H, CH_2), 3.99 (t, 2H, CH_2), 4.44 (t, 2H, CH_2), 7.14-8.16 (m, 4H, Ar-H); ^{13}C nmr (25 MHz, DMSO-d_6): 20.5, 40.2, 66.19, 117.5, 123.7, 124.9, 126.0, 134.2, 147.7, 151.1, 161.8; ms: m/z 202 (M^+), 187, 146, 119, 90.

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