Reactions of 2-Aminothiobenzamide with Isocyanates: A New Synthesis of 2,3-Dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one and 3,4-Dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one

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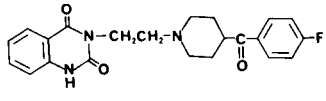
Received November 10, 1988

2-(2-Chloroethylureido)- and 2-(3-chloropropylureido)thiobenzamides **5a,b** were prepared in good yields by treating 2-aminothiobenzamide with 2-chloroethyl and 3-chloropropyl isocyanates respectively. Subsequent treatment of compound **5a** and **5b** either with alkali or mineral acid led to the formation of 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one **7a** and 3,4-Dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one **7b**.

J. Heterocyclic Chem., **26**, 595 (1989).

As part of our study to prepare bioisosteric congeners of antihypertensive ketanserine **1** [1], we reported the reaction of anthranilamide with chloroalkyl isocyanates, where 3-(chloroalkyl)-2,4-dioxo-1*H*,3*H*-quinazolines **2** were formed *via* an intermediate of 2-(chloroalkylureido)benzamide **3** [2]. In order to extend the scope of this synthetic method, we attempted to synthesize 3-(chloroalkyl)-4-thioxo-1*H*,3*H*-quinazolin-2-ones **6** from 2-aminothiobenzamide **4** and chloroalkyl isocyanate through the possible intermediates, 2-(chloroalkylureido)thiobenzamides **5**.



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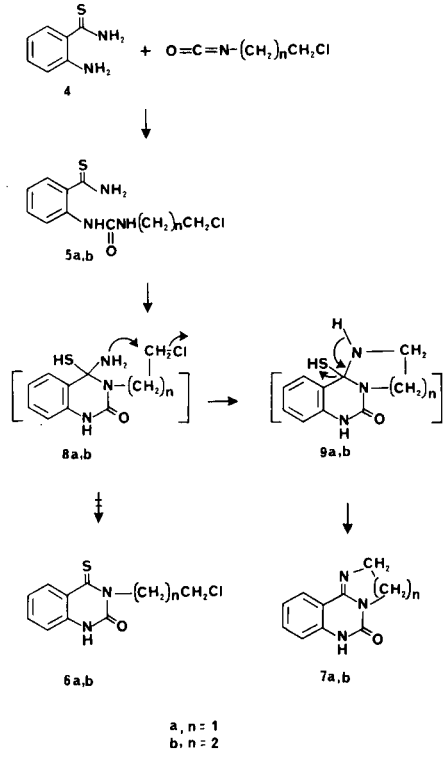
The starting material 2-aminothiobenzamide **4** [3] was prepared from anthranilamide by heating with ammonium sulfide in a sealed vessel. Treating **4** with 2-chloroethyl isocyanate afforded 2-(2-chloroethylureido)thiobenzamide **5a** in 83% yield. Compound **5a** was then treated with 10% sodium hydroxide or concentrated hydrochloric acid either at room temperature or at reflux. a single product was isolated from the reaction mixture and the structure of this product was determined to be 2,3-dihydroimidazo-[1,2-*c*]quinazolin-5(6*H*)-one **7a** instead of **6a** based on ^{1}H-, ^{13}C-nmr, mass spectral data and elemental analysis.

The mechanism of this reaction might be anticipated as an initial nucleophilic attack of the nitrogen of the ureido moiety to the sp^{2} carbon of the thiobenzamide to form an intermediate tetrahedral carbon **8**. According to our previous observation for the formation of 3-(chloroalkyl)-2,4-dioxo-1*H*,3*H*-quinazolines from 2-(chloroalkylureido)-benzamide [4], the immediate elimination of the amino group from intermediate **8** would be expected to occur and to lead to the formation of compound **6**. However, instead of this, it subsequently underwent a nucleophilic displacement between the amino group of the tetrahedral carbon



a, n = 1
b, n = 2

and the chlorine atom of the side chain to form **9** followed by elimination of hydrogen sulfide under the action of alkali or acid to give **7**.

A perusal of the literature revealed that **7a** had been synthesized either from methyl 2-ethoxycarbonylaminobenzoate and 2-aminoethylammonium-*p*-toluenesulphonate [5] or from anthranilonitrile and 2-chloroethyl isocyanate [6]. However, to our best knowledge, the method described herein has not been reported.

Repeating the above reaction using 3-chloropropyl isocyanate in place of 2-chloroethyl isocyanate gave 2-(3-chloropropylureido)thiobenzamide **5b** in 61% yield and 3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one **7b** in 85% yield respectively. It thus suggested that the reaction

described above provides an efficient synthetic method for the preparation of allied condensed derivatives of such quinazolinone.

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 ^{1}H- and ^{13}C-nuclear magnetic resonance spectra were measured on a Bruker Model AM-300 WB spectrometer at National Taiwan University, Taipei, using DMSO-d_6 or perdeuterioacetic acid as solvent and as internal standard. Mass spectra were obtained on a Finnigan MAT TSQ-46C GC/MS spectrometer at National Taiwan University. Elemental analysis was carried out on Perkin-Elmer 240 Elemental Analyzer in National Taiwan University.

2-Aminothiobenzamide (**4**).

A mixture of 2-aminobenzonitrile (40 g, 0.34 mole), ammonium sulfide (100 ml) in isopropyl alcohol (80 ml) in a sealed steel vessel was heated at 90° for 52 hours. The mixture was then concentrated *in vacuo* (water pump) to a residue. The residue was suspended in chloroform (15 ml). The solid was collected by filtration, washed with ether and recrystallized from a mixture of ethanol and benzene to afford 24 g (46%) of crystals, mp 118°; ^{1}H nmr (300 MHz, DMSO-d_6): δ 9.63 (s, 1H, NH, thioamide moiety), 9.3 (s, 1H, NH, thioamide moiety), 7.1 (m, 2H, Ar-H), 6.7 (d, 1H, Ar-H), 6.5 (t, 1H, Ar-H), 6.2 (s, 2H, NH_2); ^{13}C-nmr (75 MHz, DMSO-d_6): δ 200.0, 147.1, 130.7, 126.9, 123.7, 116.5, 115.1.

Anal. Calcd. for $C_7H_8N_2S$: C, 55.27; H, 5.27; N, 18.43. Found: C, 55.37; H, 5.22; N, 18.48.

2-(2-Chloroethylureido)thiobenzamide (**5a**).

A mixture of **4** (0.5 g, 3.0 mmoles) and 2-chloroethyl isocyanate (0.4 ml, 4.5 mmoles) in acetonitrile (5.0 ml) was stirred at room temperature for 24 hours. The solid was then collected by filtration and recrystallization from ethanol and water to give 0.7 g (83%) of **5a** mp 153° (softening); ir (potassium bromide): 3307, 3145, 1640, 1603, 1552, 1316, 1284 cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 3.3 (t, 2H, CH_2), 3.6 (t, 2H, CH_2), 7.0 (t, 1H, Ar-H), 7.2-7.3 (m, 2H, Ar-H), 7.4 (t, 1H, NH), 8.0 (d, 1H, Ar-H), 8.6 (s, 1H, NH), 9.6 (s, 1H, NH, thioamide moiety), 10.0 (s, 1H, NH, thioamide moiety); ^{13}C-nmr (75 MHz, DMSO-d_6): 41.4, 44.1, 121.1, 121.2, 126.6, 129.2, 131.9, 135.8, 154.8, 200.0; ms: m/z 257 (M^+).

Anal. Calcd. for $C_{10}H_{12}ClN_3SO$: C, 46.60; H, 4.69; N, 16.30. Found: C, 46.49; H, 4.42; N, 16.33.

2-(3-Chloropropylureido)thiobenzamide (**5b**).

Compound **5b** was prepared in 61% yield using a procedure described above. An analytical sample was obtained by recrystallization from ethyl acetate, mp 150°; ir (potassium bromide): 3287, 3122, 1630, 1568, 1315, 1283, 1229, 946 cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 1.6 (m, 2H, CH_2), 3.2 (q, 2H, CH_2), 3.7 (t, 2H, CH_2), 6.9 (t, 1H, Ar-H), 7.16-7.23 (m, 2H, Ar-H), 7.3 (t, 1H, NH), 8.0 (d, 1H, Ar-H), 8.5 (s, 1H, NH), 9.6 (s, 1H, NH, thioamide moiety), 10.0 (s, 1H, NH, thioamide moiety); ^{13}C-nmr (75 MHz, DMSO-d_6): 32.5, 36.6, 43.0, 120.9, 121.0, 126.5, 129.3, 131.6, 136.1, 154.9, 200.0; ms: m/z 271 (M^+).

Anal. Calcd. for $C_{11}H_{14}ClN_3SO$: C, 48.62; H, 5.19; N, 15.46. Found: C, 48.60; H, 5.25; N, 15.41.

2,3-Dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**7a**).

Method A.

A mixture of **5a** (1.0 g, 3.9 mmoles) in 10% sodium hydroxide solution (10 ml) was stirred in steam bath for two minutes until a clear solution had been obtained. The reaction mixture was filtered into an adapter containing water (60 ml) to get a precipitate. The solid was then collected by filtration and washed with water until the filtrate was neutral. An analytical sample was obtained by recrystallization from ethanol to yield 0.39 g (52%), mp 297° (lit [5] mp 289-292°); ir (potassium bromide): 3526, 3469, 3212, 3153, 3031, 2935, 2875, 1690, 1630, 1479, 1461, 1450, 1420, 1364, 1285, 746 cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 3.8 (m, 2H, CH_2), 3.9 (m, 2H, CH_2), 7.0-7.7 (m, 4H, Ar-H), 10.48 (s, 1H, NH). ^{13}C-nmr (75 MHz, DMSO-d_6): δ 43.62, 52.96, 111.33, 115.10, 122.16, 125.68, 133.10, 139.93, 148.32, 153.08; ms: m/z 187 (M^+).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.84; N, 22.45. Found: C, 64.08; H, 4.83; N, 22.45.

Method B.

To a mixture of **5a** (1.0 g, 3.9 mmoles) in ethanol (5 ml) was added 23% ammonia water (5 ml). The mixture was stirred at room temperature for 12 hours. The solid was then collected by filtration to give 0.66 g (93%) of compound **7a**.

Method C.

To a mixture of **5a** (2.0 g, 7.0 mmoles) in ethanol (20 ml) was added concentrated hydrochloric acid (15 ml). The mixture was then refluxed for 30 minutes. After cooling, the solid was collected by filtration to give 0.82 g (58%).

3,4-Dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one (**7b**).

Compound **7b** was prepared using a procedure similar to method A. An analytical sample was obtained by recrystallization from a mixture of ethanol and acetone to yield 0.66 g (85%) mp 247°; ir (potassium bromide): 3151, 3060, 2904, 1690, 1613, 1489, 1465, 1400, 1367, 1333, 1296, 1185, 1100, 977, 772, cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 1.8 (m, 2H, CH_2), 3.4 (t, 2H, CH_2), 3.7 (t, 2H, CH_2), 7.0-8.0 (m, 4H, Ar-H), 10.6 (s, 1H, NH); ^{13}C-nmr (75 MHz, perdeuterioacetic acid): δ 18.3, 40.9, 42.6, 108.7, 117.4, 125.8, 126.2, 138.2, 139.3, 148.9, 156.4; ms: m/z 201 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.65; H, 5.48; N, 20.91.

Acknowledgement.

This investigation was supported by a Grant from National Science Council of the Republic of China.

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