A Novel Ring Closure to Furo[2,3-b]quinoxaline [1, 2]

Adel Amer* [3], Montserrat Ventura [4], and Hans Zimmer**
University of Cincinnati, Department of Chemistry, Cincinnati, Ohio 45221, USA


3-(1-Halo-2-oxo-2-substitutedethyl)-2(1H)quinoxalinones, Furo[2,3-b]quinoxalines

An efficient method for the synthesis of furo[2,3-b]quinoxalines has been devised. Thus, 3-halo-2-arylfuro[2,3-b]quinoxalines, 5a-5c were synthesized by the action of conc. H$_2$SO$_4$ on 3-(1-halo-2-oxo-2-arylethyl)-2(1H)quinoxalinones, 3b, 3c and 3f respectively. When 3-(1-halo-2-oxo-2-substitutedethyl)-2(1H)quinoxalinones 3d and 3e (substituent = t-butyl, ethoxy) were utilized in this reaction 3-halomethylene-2(1H)quinoxalinone 6a and 6b were obtained in high yield.

Introduction

In our efforts to synthesize linearly condensed heterocyclic ring systems [5, 6] attempts were made to obtain the furo[2,3-g]pteridine system by reacting a-keto-γ-butyrolactones with 1,2-diaminoarenes as model system for the achievement of the desired heterocyclic system (Scheme 1).

This ring closure, though in complete analogy to our earlier reported synthesis of the furo[2,3-b]quinoline [5a–e] and the pyrrolo[2,3-b]quinoline [5d] systems did not occur. Instead of the expected ring closure products we isolated in good yields 3-substituted-3,4-dihydro-2(1H)quinoxalinones (1).[6] These compounds are formed by splitting off of formaldehyde in a retroaldol condensation occurring during the reaction of the a-keto-β-aryl(acyl)-γ-butyrolactones with phenylenediamine [6]. The present paper reports on attempts to use type 1 compounds to achieve the desired ring closure.

Result and Discussion

As was shown in a previous paper [6] various obvious experiments to synthesize the desired linearly condensed cyclic system met unexpectedly with failure. In attempts to utilize type 1 compounds as readily available starting materials for achieving the desired cyclization and also explore some of the chemistry, they were treated with NBS, (NCS) or elemental bromine. These compounds have three
potential sites for bromination or chlorination, respectively, with these reagents, namely both nitrogen atoms and the side chain methylene group.

To obtain a model compound for the spectroscopical identification of the bromination (chlorination) site of the type 1 compounds, 3-phenacylidene-3,4-dihydro-2H-1,4-benzoxazine-2-one (2) was chosen. After two hours of refluxing 2 with NBS in carbon tetrachloride compound 3a was isolated in form of pale yellow crystals. Its elemental analysis agreed with the formula C16H10BrNO3. The 1H NMR spectrum (CCl4) showed a singlet at δ 6.55 (1H, CHBr) and a multiplet at 7.07-8.2 (9H, ArH); suggesting that 3a is 3-(1-bromo-2-oxo-2-phenyl-ethyl)-2H-1,4-benzoxazin-2-one (Scheme 2).

Scheme 2

In every case treating 1a-1d, analogously with NBS or NCS gave one product only, namely compounds 3b-3g, respectively (Scheme 2). The 1H NMR spectrum of each of these compounds in dimethyl sulfoxide-d6 displayed a deshielded sharp signal but not a shielded one compared to the =CH signal of the parent molecule (1). These compounds also were characterized by A) a positive KI-starch test and B) debromination by refluxing with N,N-dimethylformamide and subsequent quenching with water. These facts seem to indicate that a N-halogenation did indeed occur.

However, conclusive evidence of compounds 3a-3g to be C-halogenated species rather than the N-halogenated isomers 4 is provided by 13C NMR spectroscopy. The 75.5 MHz proton decoupled 13C NMR spectrum (Me2SO-d6) of 1a (starting material) has lines at 188.259, 155.564, 145.479, 138.499, 131.778, 128.612, 126.878, 126.574, 123.963, 123.853, 123.540, 116.433, 115.234, and 88.990 ppm. The latter peak is attributed to the resonance of the olefinic carbon-atom C-1'. The 13C NMR spectrum (Me2SO-d6) of the brominated compound 3b showed signals at δ 190.078, 152.212, 152.815, 134.005, 133.582, 132.153, 131.272, 131.120, 128.799, 128.660, 123.740, 115.602, and 50.970. The up field shift of the C-1' atom from 89.0 (1J = 165 Hz) to 51.0 (1J = 154 Hz) is quite significant and lends additional support to the C-brominated structure. Also 13C NMR spectra of compound 3b in carbon tetrachloride and 3c in dimethyl sulfoxide-d6 exhibit the resonance of this carbon-atom (C-1') at δ 47.5 (1J = 152.0 Hz) and 50.6 (1J = 153.8 Hz) respectively. Compound 3b was also found to be the only product when 1a was treated with elemental bromine in acetic acid or NBS in moist N,N-dimethylformamide [7].
In further pursuit of the original goal, namely the synthesis of the furo[2,3-b]quinoxaline system, type 3 compounds were treated with conc. sulfuric acid and depending on R, different results were obtained. When R is an aryl group the desired system was formed and compounds 5a, 5b and 5c were obtained (Scheme 3). However, when R is t-butyl or ethoxy, 3-halomethylene-2(1H)quinoxalinones, 6a and 6b were isolated (Scheme 4).

To explain the difference in the results it is assumed that the intermediate carbocation in the case R = Ar is more stabilized than with R = Alkyl, or OEt. Thus, the base in the case R = Ar rather attacks and abstracts the N–H atom of the ring followed by an attack of the quinoxalinone oxygen atom at the carbocation (Scheme 3). In the case with R = t-butyl and OEt the less stabilized carbocation is more electrophilic than the N–H atom of the ring. Consequently attack of the base occurs at this site resulting in a C–C bond cleavage (Scheme 4). It is well known that type 1 compounds undergo, by the action of PPA or a POCI3/PCl5 mixture, a dehydrative cyclization to give furo[2,3-b]quinoxalines [8]. Our attempts, however, to cyclize type 1 compounds by treating them with conc. H2SO4 at 70 °C resulted only in recovery of starting material.

**Experimental**

**General:** Melting points were determined with a Fischer-Johns and/or Melt-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 599 spectrometer calibrated against 1601 cm⁻¹ band of polystyrene. ¹H NMR spectra were recorded on a Varian T-60 spectrometer. ¹³C NMR spectra were recorded on a Nicolet NT 300 narrow-bore spectrometer (75.5 MHz) with an 1180 E data system. Chemical shifts are expressed in δ relative to tetramethylsilane as internal standard and coupling constants (J values) in Hertz. MS data were obtained on a Perkin-Elmer RMU-7 mass spectrometer and/or a Kratos MS 80 instrument with a DS-55 data system. Elemental analyses were performed at M–H–W Laboratories, Phoenix, Arizona.

**3-Phenacylidene-3,4-dihydro-2H-1,4-benzoxazin-2-one (2)**

The preparation was done essentially as reported earlier [9]; a mixture of 1.1 g of o-aminophenol with ethyl benzoylpyruvate was heated at 80–100 °C for 15 min to result in a solid product which was recrystallized from methanol; yield = 70%; m.p. = 205 °C (lit. [9] m.p. = 201 °C).

MS m/e calcd. for M⁺, (C₁₆H₁₁NO₃); m/e 265.07393. Found: m/e 265.0729.

**3-(1-Bromo-2-oxo-2-phenylethyl)-2H-1,4-benzoxazin-2-one (3a)**

To a hot suspension of 1 g of 2 in 300 ml carbon tetrachloride was added 0.65 g N-bromosuccinimide (NBS) and refluxed for 2 h. The reaction mixture was left overnight and filtered by suction. The filtrate was then concentrated and left to evaporate in the hood at room temperature. The residue was recrystallized from methanol; m. p. = 105 °C; ¹H NMR (CCl₄) δ 6.55 (s, 1H, CHBr), 7.07–8.2 (m, 9H, ArH).

Anal. calcd. for C₁₆H₁₅BrNO₂: Br 23.22; found: Br 23.21.

**3-(1-Halo-2-oxo-2-substitutedethyl)-2(1H)-quinoxalinone (3b–3g)**

**General method**

A) To a hot suspension of 0.004 mole of type 1 compound in 350 ml CCl₄ was added an equivalent
amount of NBS (or NCS) and refluxed for 1–2 h. The original yellow suspension turned white during the reaction. The solid residue was filtered off while the solution was hot. For purification the material was recrystallized from methanol.

B) A solution of 0.004 mole of type 1 compound in 25 ml N,N-dimethylformamide and 0.4 ml water was warmed to 57 °C when 0.004 mole of NBS (or NCS) was added. The reaction mixture was left overnight and poured onto 150 ml of cold water. The material that precipitated was filtered off, washed with cold methanol and dried. It was found to be identical with that prepared by method A.

3-(1-Bromo-2-oxo-2-phenylethyl)-2(1H)-quinoxaline (3b)

Yield = 67% and 95.4% (method A and B respectively); m.p. = 228 °C (MeOH); IR (KBr) 3200–2500, 1655 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 7.13 (s, 1H, CHBr), 7.4–8.0 (m, 6H, ArH), 12.6 (s, 1H, NH is D₂O exchangeable); MS 432, 344 (Mr; Mr + 2) (RI = 2.6, 2.3%), 264 (47.9), 263 (10.3), 255 (25.9), 187 (18.2), 186 (2.9), 159 (15.9), 131 (10.4), 105 (100), 82 (13.3), 81 (48), 80 (13.9), 79 (5.0).

Anal. calced. for C₁₈H₁₉BrN₂O₂: C 55.97; H 3.23; Br 23.3.

Compound 3b also was obtained in 95% yield by adding 1 ml of Br₂ to a suspension of 1 g of 1a in 25 ml glacial acetic acid. The reaction mixture was left at −20 °C for 5 h. After reaching room temperature water was added; the resulting precipitate was filtered, washed with water and cold methanol and dried. The obtained compound proved to be 3b and was identical with that prepared by the previous methods.

3-(1-Bromo-2-oxo-2-(3,4-dimethoxyphenyl)ethyl)-2(1H)-quinoxaline (3c)

Yield = 79% (method A); m.p. = 221 °C (MeOH); IR (KBr) 3200–2500, 1680, 1655 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 3.67, 3.70 (2 s, 6H, OCH₂), 6.53 (s, 1H, CHBr and ArH), 12.6 (s, 1H, NH is D₂O exchangeable); MS 402, 340 (Mr; Mr + 2) (RI = 1.47, 1.51%), 224 (66.9), 296 (2.7), 295 (8.5), 187 (15.3), 186 (17.1), 165 (100), 159 (11.5), 138 (92.8), 123 (11.0), 107 (8.5), 82 (19.8), 81 (7.2), 80 (21.7), 79 (2.3).

Anal. calced. for C₁₉H₁₉BrN₂O₃: C 53.51; H 3.75; N 6.95; found: C 53.23; H 4.14; N 6.70.

3-(1-Bromo-2-oxo-3,3-dimethylbutyl)-2(1H)-quinoxaline (3d)

Yield = 67% (method A); m.p. = 195–196 °C (MeOH); IR (KBr) 3200–2500, 1700, 1660 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 1.1 (s, 9H, C(CH₃)₃), 6.5 (s, 1H, CHBr), 7.2–7.8 (m, 4H, ArH), 12.6 (s, 1H, NH is D₂O exchangeable); MS 522, 324 (Mr; Mr + 2) (RI = 0.98, 0.78%), 244 (8.6), 238 (4.4), 187 (59.1), 159 (12.0), 131 (12.8), 103 (8.8), 85 (47.3), 82 (9.9), 81 (3.00), 80 (9.8), 79 (2.6).

Anal. calced. for C₁₉H₂₃BrN₂O₂: C 52.02; H 4.68; Br 24.73; found: C 52.01; H 4.71; Br 24.85.

Ethyl-2-bromo-2-(2(1H)quinoxalinon-4-yl)-acetate (3e)

Yield = 68% (method A); m.p. = 208 °C (MeOH); IR (KBr) 3020–2700, 1754, 1665 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 1.07 (t, 3H, OCH₂CH₃), 4.13 (q, 2H, OCH₂CH₃), 5.97 (s, 1H, CHBr), 7.1–7.9 (m, 4H, ArH), 12.7 (s, 1H, NH is D₂O exchangeable); MS 310, 312 (Mr; Mr + 2) (RI = 8.7, 7.5%), 267 (1.9), 266 (2.1), 265 (2.6), 264 (2.4), 253 (1.2), 251 (1.0), 240 (6.9), 239 (13.2), 238 (6.8), 237 (13.5), 232 (6.5), 231 (5.5), 212 (1.5), 211 (9.2), 210 (2.0), 209 (11.8), 187 (12.7), 186 (11.6), 175 (21.9), 159 (48.6), 158 (19.0), 157 (9.8), 147 (13.1), 132 (13.3), 131 (40.2), 130 (30.1), 129 (20.5), 104 (10.5), 103 (61.8), 102 (36.2), 90 (70.1), 82 (8.3), 81 (3.3), 80 (9.2), 79 (7.9).

Anal. calced. for C₁₂H₁₂BrN₂O₂: C 46.32; H 3.56; found: C 46.41; H 3.64.

3-(1-Chloro-2-oxo-phenylethyl)-2(1H)-quinoxaline (3f)

Yield = 69.4% and 97.6% (method A and B respectively); m.p. = 220–222 °C (MeOH); IR (KBr) 3200–2580, 1715, 1675 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 7.03 (s, 1H, -CHCl), 7.3–7.9 (m, 9H, ArH), 12.7 (s, 1H, NH is D₂O exchangeable), MS (Mr; Mr + 2) 298, 300 (RI = 1.6%, 0.5), 264 (67.5), 235 (22.3), 187 (22.8), 160 (18.1), 131 (10.7), 105 (100).

Anal. calced. for C₁₃H₁₂ClN₂O₂: C 64.33; H 3.71; N 9.37; found: C 64.28; H 3.74; N 9.39.

3-(1-Chloro-2-oxo-3,3-dimethylbutyl)-2(1H)-quinoxaline (3g)

Yield = 61% (method A); m.p. = 217 °C (MeOH); IR (KBr) 3200–2500, 1710, 1670 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 1.2 (s, 9H, C(CH₃)₃), 6.53 (s, 1H, CHCl), 7.2–7.93 (m, 4H, ArH), 12.7 (s, 1H, NH is D₂O exchangeable); MS (Mr; Mr + 2) 278, 280 (RI = 3.27%, 0.97), 244 (7.2), 242 (3.3), 201 (1.1), 196, 194 (16.5, 61.7), 187 (61.5), 167, 165 (2.4, 5.5), 159 (11.9), 131 (28.5), 103 (18.7), 102 (11.8), 90 (20.1), 85 (68.3), 77 (11.0), 76 (11.2), 57 (100).

Anal. calced. for C₁₄H₁₃ClN₂O₂: C 60.32; H 5.42; Cl 12.72; found: C 60.37; H 5.40; Cl 12.90.

Reaction of type 3 compounds with conc. H₂SO₄

General procedure: To 0.01 mole of a type 3 compound was added 20 ml of conc. sulfuric acid. After heating the reaction mixture at 60–70 °C for a 4 h period on a water-bath it was poured onto crushed ice. The precipitate was filtered off, washed with water and dried.

3-Bromo-phenylfuro[2,3-b]quinoxaline (3a) [11]

It was prepared by the action of conc. H₂SO₄ on 3-(1-bromo-2-oxo-2-phenylethyl)-2(1H)quinoxaline-
none, 3b; yield = 90.5%; m.p. = 175 °C (MeOH) (lit. [10] m.p. = 175 °C); 1H NMR (CDCl3) δ 7.47 to 8.40 (2m, 9 H, ArH); MS 324, 325, 326, 327 (M+, M+1, M+2, M+3) (RI = 100, 19.9, 99.5, 17.98%), 246 (16.4), 245 (22.8), 217 (20.6), 190 (7.1), 168 (8.4), 122 (17.2), 105 (28.6), 90 (41.9).

Anal. calcd. for C18H13BrN2O: Br 24.58; found: Br 24.69.

3-Bromo-2-(3,4-dimethoxyphenyl)furo[2,3-b]quinoxaline (5b)

Analogously in a yield of 86% by the reaction of 3-[1-bromo-2-oxo-2-(3,4-dimethoxyphenyl)ethyl]-2(1H)quinoxalinone, 3c with conc. H2SO4; m.p. = 224 °C (MeOH); MS 384, 385, 386, 387 (M+, M+1, M+2, M+3) (RI = 16.1, 6.2, 24.9, 13.6%), 306 (13.6), 278 (10.6), 262 (13.2), 228 (11.4), 165 (5.9), 135 (10.3).

Anal. calcd. for C18H14BrNaOs: C 56.12; H 3.40; Br 20.75; found: C 56.30; H 3.60; Br 20.66.

3-Chloro-2-phenylfuro[2,3-b]quinoxaline (5c)

Analogously in a yield of 92%, by the reaction of 3-(1-chloro-2-oxo-2-phenylethyl)-2(1H)quinoxalinone, 3f with conc. H2SO4; m.p. = 180 °C (MeOH); MS 280, 281, 282, 283 (M+, M+1, M+2, M+3) (RI = 100.0, 22.2, 39.3, 8.2%), 252 (5.0), 246 (9.2), 245 (7.9), 217 (15.6), 105 (29.6), 90 (32.2).

Anal. calcd. for C18H13ClN2O: Cl 12.63; found: Cl 12.71.

3-Bromomethylene-2(1H)quinoxalinone (6a)

Analogously in a yield of 90%, by the action of conc. H2SO4 on 3d or 3e; m.p. = 230 °C (decomp.) (MeOH); IR (KBr) 2820, 1655 cm⁻¹; 1H NMR (Me2SO-d6) δ 4.48 (s, 2H, CH2Br), 7.47 (m, 4H, ArH), 12.8 (s, 1H, NH is D2O exchangeable); MS 238, 239, 240, 241 (M+, M+1, M+2, M+3) (RI = 21.4, 3.35, 25.6, 2.7%), 160 (22.3), 159 (40.7), 131 (100).

Anal. calcd. for C9H7BrN2O: Cl 33.43; found: Cl 33.31.

3-Chloromethylene-2(1H)quinoxalinone (6b)

It was prepared analogously in a yield of 90% by the reaction of 3g with conc. H2SO4; m.p. = 230 °C (decomp.) (MeOH); IR (KBr) 2840, 1670 cm⁻¹; 1H NMR (Me2SO-d6) δ 4.77 (s, 2H, CH2Cl), 7.5 (m, 4H, ArH), 12.6 (s, 1H, NH is D2O exchangeable); MS 194, 195, 196, 197 (M+, M+1, M+2, M+3) (RI = 86.8, 10.5, 39.6, 7.4%), 160 (22.3), 159 (40.7), 131 (100).

Anal. calcd. for C9H7ClN2O: Cl 18.22; found: Cl 18.11.