Synthesis of Benzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones from Anthranilic Acid and 1,2-Diaminobenzene

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Abstract

1,2-Diaminobenzene adds to hydrazonoyl chlorides derived from anthranilic acid to yield 2-(2-(3-oxo-3,4-dihydroquinoxalin-2(1H)ylidene)hydrazinyl)benzoic acids 8. The latter compounds cyclize to the corresponding benzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones upon treatment with carbonyldiimidazole 9.

Keywords: Benzotriazepine; 1,2,4-Triazepino[4,3a]quinoxaline-6,13(5H,8H)diones; Anthranilic acid; Diaminobenzene; Carbonyldiimidazole.

Introduction

The benzotriazepine heterocyclic nucleus encompasses a number of isomers, of which benzo-1,3,4-triazepines, and to a lesser extent benzo-1,3,5-triazepines and benzo-1,2,5-triazepines, are the most common in the chemical literature. The chemistry of these heterocyclic systems is a subject of continuing interest due to their potential and diverse pharmacological activities, which include, among others, antibacterial [1,2] antifungal [2,3], anti-inflammatory [4], antidepressant and sedative effects [5].

Furthermore, some triazepine derivatives have been found useful in treatment of gastric acid related disorders [6], and in the prevention of nervous system-related disorders, such as Parkinson and Alzheimer diseases [7], while others might find possible application in the chemotherapy of certain types of cancer [8,9]. Incorporation of additional heterocyclic ring in the benzotriazepine pharmacophore, seems to enhance the biological activity of these compounds [10].

Whereas synthetic methods for 1,3,4-benzotriazepines are abundant in the literature [9,11], methods for the construction of the other benzotriazepines, particularly the 1,2,4-analogs are so far limited [12, 13].

Experimental Section

General

2-Aminobenzoic acids, carbonyldiimidazole (CDI), and all solvents were purchased from Aldrich Chemical Company, and 1,2-diaminobenzene was from Fluka. THF was dried over sodium and then distilled just before use. Melting points were
measured on Phillip Harris melting point apparatus and were uncorrected. ¹H- and ¹³C-
NMR spectra were measured on a Bruker DPX-300 instrument, and chemical shifts
are expressed in ppm with reference to TMS as internal reference. Infrared spectra
were recorded as potassium bromide (KBr) discs on a Nicolet Impact-400 FTIR
spectrophotometer. High resolution mass spectra (HRMS) were measured in either
positive or negative ion mode by Electrospray Ionization (ESI) on a Bruker Apex IV
instrument. Samples were dissolved in acetonitrile, diluted in spray solution (methanol /
water 1:1 v/v + 0.1% formic acid) and infused using a syringe pump at a flow rate of 2
µL/min. External calibration was performed in the mass range m/z 175-871 using
arginine cluster ions.

Preparation of hydrazonoyl chlorides 4a-c and 4'.

To a cold solution (0-5 °C) of 2-aminobenzoic acid (0.1 mol) in aqueous
hydrochloric acid (80 mL, 5M), a solution of sodium nitrite (7.6 g, 0.12 mol) in water (20
mL) was added dropwise with continuous stirring. The solution was stirred further for
20-30 min. at 0-5 °C. To this solution, a cold solution of methyl chloroacetylacetone 3
(or chloroacetoacetate 3') (0.1 mol) and 16.4 g sodium acetate (0.2 mol) in ethanol
(200 mL) was then added in one portion. The resulting mixture was stirred for 20 min,
diluted with cold water (100 mL), and the solid product was then collected by filtration,
washed with water and recrystallized from ethanol.

2-(2-(1-Chloro-2-methoxy-2-oxoethylidene)hydrazinyl)benzoic acid 4a. Yield 86%;
yellow solid; m.p. 209-210 °C (Lit. ¹² m.p. 215-216 °C).

4-Chloro-2-(2-(1-chloro-2-methoxy-2-oxoethylidene)hydrazinyl)benzoic acid 4b. Yield
94%; yellow solid; m.p. 262-263 °C. IR (KBr) ν (cm⁻¹): 3450, 3150, 1727, 1678, 1639.
HRMS (ESI): m/z calc. for [M-H]⁻ 288.97883; found 288.97884. ¹H NMR (DMSO-d₆) δ
(ppm): 3.35(s, 3H, OCH₃), 7.12 (dd, 1H, H-5), 7.56 (d, 1H, H-3), 7.94 (d, 1H, H-6),
12.20 (s, NH), 13.80 (brs, CO₂H). ¹³C NMR (DMSO-d₆) δ (ppm): 54.2 (OCH₃), 112.7
(C-1), 113.9 (C-3), 119.4 (C-4), 121.9 (C-5), 133.9(C-6), 139.8 (C-2), 145.5 (C=N),
159.6 (ester C=O),169.3 (CO₂H).

2-(2-(1-Chloro-2-methoxy-2-oxoethylidene)hydrazinyl)-5-nitrobenzoic acid 4c. Yield
85%; yellow solid; m.p. 244-245 °C. IR (KBr) ν (cm⁻¹): 3480, 3360, 1681, 1622, 1563.
HRMS (ESI): m/z calc. for [M-H]⁻ 300.00289; found 300.00289. ¹H NMR (DMSO-d₆) δ
(ppm): 3.83 (s, 3H, OCH₃), 7.51 (d, 1H, H-3), 8.31 (dd, 1H, H-6), 8.54 (d, 1H, H-4),
12.15 (s, NH), 14.00 (brs, CO₂H). ¹³C NMR (DMSO-d₆) δ (ppm): 54.3 (OCH₃), 113.2
(C-1), 115.2 (C-3), 121.9 (C-5), 127.6 (C-6), 129.9 (C-4), 140.7 (C-2), 148.5 (C=N),
159.3 (ester C=O), 168.3 (CO₂H).

2-(2-(1-Chloro-2-oxopropylidene)hydrazinyl)benzoic acid 4'. Yield 91%; yellow solid;
m.p. 243-245 °C. IR (KBr) ν (cm⁻¹): 3460, 3210, 1740, 1697, 1668. HRMS (ESI) m/z
calc. for [M-H]⁻ 239.02289; found 239.02289. ¹H NMR (DMSO-d₆) δ (ppm): 2.47 (s, 3H,
CH₃), 7.11 (t, 1H, H-5), 7.64 (t, 1H, H-4), 7.75 (d, 1H, H-3), 7.96 (d, 1H, H-6), 12.00 (s, NH), 13.75 (brs, CO₂H). ¹³C NMR (DMSO-d₆) δ (ppm): 25.9 (CH₃), 113.9 (C-1), 114.9 (C-3), 122.3 (C-5), 126.9 (C-2), 131.9 (C-6), 135.4 (C-4), 144.3(C=N), 170.0 (CO₂H), 188.4 (acetyl C=O).

Preparation of compounds 8a-c, 8'.

A mixture of the hydrazonoyl chloride 4 or 4' (5 mmol), 1,2-diaminobenzene (5 mmol) and triethylamine (6 mmol) in ethanol (50 mL) was refluxed for 12 h. The precipitate formed upon cooling was collected by filtration, washed with water and recrystallized from DMF / water.

2-[2-(3-Oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)hydrazino]benzoic acid 8a. Yield 53%; yellow solid; m.p. 294-295 ºC. IR (KBr) ν (cm⁻¹): 3480, 3340, 3190, 3160, 1664, 1611, 1573. HRMS (ESI) m/z calc. for [M-H] - 295.08366; found 295.08366. ¹H NMR (DMSO-d₆) δ (ppm): 6.84 (t, 1H, H-5'), 7.06-7.39 (m, 6H, H-6', H-4', H-3', H-6, H-7 , H-8), 7.84-7.86 (d, 1H, H-5), 9.29 (s , NH), 9.65 (s, NH), 12.32 (brs, CO₂H). ¹³C NMR (DMSO-d₆) δ (ppm): 111.9 (C-1'), 113.0 (C-3 '), 115.4 (C-5 '), 117.1(C-6), 123.7 (C-8), 124.8 (C-5), 125.4 (C-7), 129.0 (C-4a), 131.7 (C-6), 132.8 (C-8a), 134.7 (C-4'), 149.9 (C-2), 151.3 (C-3), 151.8 (C-3), 169.9 (CO₂H).

4-Chloro-2-[2-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)hydrazino]benzoic acid 8b. Yield 85%; yellow solid; m.p. 317-318 ºC. IR (KBr) ν (cm⁻¹): 3380, 3288, 1670, 1598. HRMS (ESI) m/z calc. for [M+H] +  331.05924; found 331.05924. ¹H NMR (DMSO-d₆) δ (ppm): 7.34-7.48 (m, 6H, H-8, H-6, H-7, H-3 ', H-5, H-5 '), 7.89 (d, 1H, H-6'), 9.65 (s, NH), 10.09 (s, NH), 12.36 (brs, CO₂H). ¹³C NMR (DMSO-d₆) δ (ppm): 111.1 (C-3), 115.4 (C-8), 116.4 (C-7), 123.6 (C-6), 124.6 (C-5), 125.4 (C-5), 129.1 (C-4a), 130.0 (C-6), 134.0 (C-8a), 137.0 (C-4'), 149.9 (C-2), 151.3 (C-3), 151.8 (C-3), 169.2 (CO₂H).

5-Nitro-2-[2-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)hydrazino]benzoic acid 8c. Yield 85%; yellow to red solid; m.p. 168-169 ºC. IR (KBr) ν (cm⁻¹): 3547, 3178, 1693, 1644, 1511. HRMS (ESI) m/z calc. for [M-H] -  340.06874; found 340.06874. ¹H NMR (DMSO-d₆) δ (ppm): 6.78-8.15 (m, 5H, H-8, H-6, H-7, H-3 ', H-5), 8.42 (d, 1H, H-4'), 8.68 (s, 1H, H-6'), 9.88 (brs, NH), 10.40 (brs, NH), 10.60 (brs, NH), 12.34 (brs, CO₂H). ¹³C NMR (DMSO-d₆) δ (ppm): 113.9 (C-3), 115.5 (C-6), 123.7(C-8), 124.4 (C-5), 125.7 (C-7), 128.5 (C-6), 129.0(C-4a), 132.5 (C-8a), 137.0 (C-5'), 149.5 (C-2'), 149.7(C-2), 151.4 (C-3), 169.1 (CO₂H).

2-[2-(3-Methylquinoxalin-2-yl)hydrazino]benzoic acid 8'. Yield 73%; yellow solid; m.p. 259-263 ºC. IR (KBr): ν (cm⁻¹): 3292, 1672, 1587, 1528, 1490. HRMS (ESI) m/z calc. for [M+H] +  347.10440; found 347.10440. ¹H NMR (DMSO-d₆) δ (ppm): 2.47(s, 3H, CH₃), 6.75 (t, 1H, H-5), 7.09 (d, 1H, H-6'), 7.33-.46 (m, 4H, H-4', H-3', H-6, H-9), 7.82 (dd, 2H, H-5, H-8), 9.23 (s, NH), 9.44 (s, NH), 13.00 (s, CO₂H). ¹³C NMR (DMSO-d₆) δ
(ppm): 21.5 (CH₃), 112.2 (C-1'), 113.2 (C-3'), 117.7 (C-5'), 125.1 (C-6), 126.3 (C-8),
128.1 (C-5), 129.2 (C-7), 131.8 (C-6'), 134.7 (C-4'), 137.4 (C-4a), 140.6 (C-8a), 145.9
(C-2), 151.1 (C-3), 152.0 (C-2), 169.9 (CO₂H).

Preparation of compounds 9a-c.

CDI (0.41 g, 2.5 mmol) was added to a cold (0 °C) and stirred solution of the
hydrazone 3 (2 mmol) in dry THF (30 mL). The resulting mixture was further stirred at
room temperature for 8 h. Cold water (20 mL) was then added and the solvent was
evaporated under reduced pressure. The solid left was washed with water, dried and
recrystallized from DMF / water.

Benzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones 9a. Yield 82%; yellow
solid; m.p. 285-287 °C (d). IR (KBr) ν (cm⁻¹): 3230, 1725 ,1635 ,1556. HRMS (ESI):
m/z calculated for [M+Na]+ 301.06959; found 301.06959. ¹H NMR (DMSO-d₆) δ (ppm):
7.16 (t, 1H, H-11), 7.36 (m, 3H, H-4, H-2, H-12), 7.65 (dd, 2H, H-3,H-9), 7.75 (t, 2H, H-
1, H-10), 10.60 (brs, NH), 12.8 (brs, NH), 113.4 (C-9), 115.9 (C-2), 116.9 (C-12a),
122.0 (C-12), 124.1 (C-10), 124.4 (C-11), 128.7 (C-4), 130.9 (C-4a), 131.2 (C-1), 132.5
(C-14a), 133.5 (C-3), 146.6 (C-8a), 148.1 (C-6a), 151.6 (C-6), 161.9 (C-13).

10-Chlorobenzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones 9b. Yield
78%; yellow solid; m.p. 305-308 °C. IR (KBr) ν (cm⁻¹): 3210, 1740, 1698. HRMS (ESI)
m/z calc. for [M+Na]+ 335.03062; found 335.03062. ¹H NMR (DMSO-d₆) δ (ppm):
7.14 (d, 1H, H-12), 7.34-7.45 (m, 3H, H-2, H-4), 7.58 (t, 1H, H-3), 7.76 (m, 2H, H-11),
11.90 (brs, 2H). ¹³C NMR (DMSO-d₆) δ (ppm): 113.0 (C-9), 115.5 (C-12a), 116.0 (C-2),
122.3 (C-12), 124.4 (C-11), 125.9 (C-4), 128.9 (C-1), 130.9 (C-4a), 131.29 (C-3), 132.6
(C-14a), 138.4 (C-10), 146.1 (C-8a), 148.6 (C-6a), 151.5 (C-6), 160.8 (C-13).

11-Nitrobenzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones 9c. Yield 72%;
yellow solid; m.p. 315-316 °C; IR (KBr) ν (cm⁻¹): 3240, 1720, 1696, 1657. HRMS (ESI)
m/z calc. for [M-H]^⁻ 322.05817; found 322.05818. No NMR could be obtained for this
compound since it was completely insoluble.

Preparation of 4-chloro- and 4-bromo-1,2-diaminobenzene.

The appropriate N-arylacetamide (65 mmol) was dissolved in concentrated sulfuric acid (35 ml) and cooled to 0-5 °C. Concentrated nitric acid (35 ml) was then added dropwise to during 1 h with stirring. Stirring of the cold mixture was continued for additional 1 h. The reaction mixture was then poured over ice-water (200 mL) and the resulting yellow precipitate was collected, washed several times with water, and dried. The crude product was dissolved in concentrated hydrochloric acid (30 mL) and ethanol (100 mL) and refluxed for 3 h. The reaction mixture was then cooled and poured onto ice-water (150 mL). The orange precipitate was collected, washed with water and dried. This solid was placed in a double-necked flask equipped with a condenser. Zinc powder (20 g), and dichloromethane (200 mL) were added, followed
by dropwise addition of acetic acid (65 mmol) in dichloromethane (100 mL) under continuous stirring of the mixture at room temperature. Stirring was continued for 2 h before excessive zinc powder was removed by filtration. The filtrate was washed with saturated sodium bicarbonate solution (2x100 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the crude product was recrystallized from chloroform / petroleum ether.

4-Chloro-1,2-diaminobenzene. Yield 48%; m.p. 75-76 °C (Lit. [15] m.p. 76-78 °C).

4-Bromo-1,2-diaminobenzene. Yield 56%; m.p. 64-67 °C (Lit. [16] m.p. 65-69 °C).

Results and Discussion

Starting with commercially available 1,2-diaminobenzene 6 and anthranilic acid 1 as main starting materials, we report here on a new facile synthesis of 1,2,4-benzotriazepines, namely benzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones 9.

We found in the present investigation that 1,2-diaminobenzene 6 reacts readily with the hydrazonoyl chlorides 4, derived from anthranilic acids 1, in the presence of triethylamine as a base, to give quinoxaline derivatives 8. The latter quinoxalines are presumably formed through intramolecular cyclization of the anticipated acyclic intermediate adducts 7, which are obviously formed through direct nucleophilic addition of 1,2-diaminobenzene to the nitrile imine intermediates 5, generated in situ through dehydrohalogenation of the corresponding hydrazonoyl chlorides 4 by the action of triethylamine. The acyclic adducts 7 could not, however, be isolated or detected in the reaction mixture, since they presumably undergo spontaneous cyclization, under the reaction conditions employed, to the hydrazones 8, which were isolated from the reaction mixtures as the main products of this reaction (Scheme 1).

![Scheme 1](image_url)

Scheme 1: Synthesis of compounds 8 from anthranilic acids and 1,2-diaminobenzene.
Subsequent treatment of the adducts 8 with carbonyldiimidazole (CDI), furnished the corresponding benzo[6,7][1,2,4]triazepino[4,3a]quinoxaline-6,13(5H,8H)diones 9 in good yields (Scheme 2).

Scheme 2: CDI-assisted cyclization of compounds 8 to 9.

The structures of compounds 9 were confirmed through their $^1$H NMR, $^{13}$C NMR, and IR spectral data, and their exact molar masses were determined by high resolution mass spectrometry (HRMS). Thus, in agreement with the assigned structures, the $^1$H NMR spectra of compounds 9 showed two broad singlets in the region of 10-14 ppm for the two NH protons, as well as a multiplet at 6.9-7.8 ppm for the aromatic protons. The COSY and HMQC experiments provided correlations which were in agreement with the assigned structures.

The occurrence of cyclization of compounds 8 into 9 was further ascertained through the IR spectra of the latter compounds, which exhibited absorptions at 3225, 1690, 1635, and 1560 cm$^{-1}$ attributed to the N-H, C=O, and C=N bond stretching modes, respectively. Unlike precursors 8, compounds 9 did not show any absorption bands in the region of 3600-3300 cm$^{-1}$, characteristic of the carboxyl OH group.

Scheme 3: Synthesis of compounds 8’ from anthranilic acid and 1,2-diaminobenzene.

In contrast to the quinoxalinone derivatives 8, which undergo facile cyclization to compounds 9 upon mild treatment with CDI, the quinoxaline derivative 8’, obtained through condensation of 1,2-diaminobenzene with the hydrazonoyl chloride 4’ (Scheme 3), did not undergo analogous cyclization with CDI under the reaction conditions.
employed for compounds 8. Prolonged treatment of compound 8' with CDI (2 days at room temperature), did not lead to the formation of any detectable reaction products, and the reaction mixture revealed only starting materials upon TLC examination. Such unforeseen behavior of compound 8' might be attributed to its tautomerization to 8'', whereby the quinoxaline ring becomes fully aromatized. However, it remains unclear, why the latter tautomeric form did not undergo alternative CDI-initiated cyclization leading to the formation of a 5-membered pyrazolidinone ring system 10 (Scheme 4).

Scheme 4: Attempted cyclization of compounds 8' and 8''.

The 1H NMR spectra of compounds 8 and 8' showed multiplets at 6.7-7.9 ppm for the aromatic protons, two broad singlets in the range 9.2-10.0 ppm attributed to the two N-H protons, and an additional broad singlet at 12.3-13.0 ppm, assigned to the CO$_2$H proton. No signal was observed in the 1H NMR spectra of compounds 8 for the ester OMe group, which appeared as a distinct singlet in the range of 3.5-3.8 ppm in the 1H NMR spectra of the starting compounds 4.

The 13C NMR spectra of compounds 8 and 8' revealed, in addition to the correct numbers and positions of signals corresponding to the aromatic carbon atoms, a signal in the range of 169.1-172.0 ppm, assigned to the CO$_2$H carbon, and two signals at 149.5-152.1 ppm, assigned to the endocyclic C=N and C=O carbons. The CH$_3$ group in compound 8' gave rise to a singlet at 2.47 ppm (3H) in the 1H NMR, and to a signal at 21.56 ppm in the 13C NMR spectrum of the compound.

The IR spectra (KBr) of compounds 8 showed a broad absorption in the region of 3500 cm$^{-1}$ and a relatively sharp absorption at about 3340 cm$^{-1}$ corresponding, respectively, to the O-H and the N-H bond stretching. The absorption due to the carbonyl C=O bond stretching appeared at about 1660 and 1620 cm$^{-1}$.

The hydrazonoyl chlorides 4 and 4' were accessible via the Japp-Klingmann reaction between the diazonium salt, generated from anthranilic acid, and chloroacetylacetone 3 (or ethyl chloroacetoacetate 3') at 0 °C in the presence of sodium acetate as a base, following literature procedure [13].
It is worth noting that analogous condensation of substituted 1,2-diaminobenzene, namely 4-bromo- and 4-chloro-1,2-diaminobenzene, with hydrazonoyl chlorides 4, under similar reaction conditions employed for the unsubstituted 1,2-diaminobenzene, resulted in excessive oxidation of the diamines, as indicated through an almost instantaneous dark blue to black coloration acquired by the reaction mixtures upon mixing of the reactants under nitrogen atmosphere and in presence of either butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA) as antioxidants. Preliminary TLC examination of the reaction mixtures revealed complex mixtures of unidentifiable, and practically inseparable products. The 4-halo-1,2-diaminobenzenes were prepared by reduction of the corresponding nitro-derivatives (Scheme 5), following literature procedure for similar compounds [14].

Scheme 5: Preparation of 4-substituted-1,2-diaminobenzenes.

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References


