Synthesis of 3-Hydroxy-3-cyclobutene-1,2-dione Based Amino Acids

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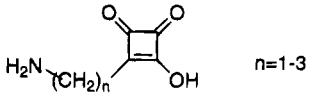
Introduction

The importance of the carboxylic acid group in molecular recognition has led to the development of many bioisosteres of this functionality. Recently the 3-hydroxy-3-cyclobutene-1,2-dione group was demonstrated to be bioequivalent to a carboxylic acid or tetrazole in an influenza RNA polymerase assay[1] and an angiotensin II assay.[2] In order to explore the generality of its use in medicinal chemistry, this carboxylic acid isostere was incorporated into the amino acids glycine, β-alanine, and γ-aminobutyric acid (**1a,b,c**). A strychnine-insensitive [^{3}H]glycine binding assay was utilized to ascertain the bioequivalence of these substrates to glycine.[3] This glycine receptor modulates activation of the NMDA receptor; antagonists at this site have potential as neuroprotective agents.[4]



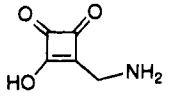
1a–c

Results and Discussion

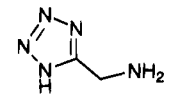
The methodology utilized to synthesize **1a–c** was based on the previously reported addition[5] of alkyl radicals to the reagent 3-isopropoxy-4-(tri-*n*-butyltin)-3-cyclobutene-1,2-dione (**2**).[6] In Scheme 1, the addition of alkyl radicals, generated from (haloalkyl)phthalimides **3a–c** and initiator **4**,[7] to **2** was achieved in toluene at 110 °C over 24–48 h. The initiator **4** was introduced at a rate of 0.15 equiv per 12 h relative to alkyl halide; 2 equiv of reagent **2** was utilized. The yield in this reaction was good in the case of the propyl radical. The ethyl radical was more difficult to generate from the bromide[5] and would be expected to be less reactive due to the radical's proximity to the electron-withdrawing phthalimide group. The ready formation and good reactivity of the methylphthalimide radical, also generated from the bromide, is based on the nitrogen lone pair donating through resonance.[8] The resultant adducts **5a,b,c** were hydrolyzed with 6 N HCl at room temperature in tetrahydrofuran overnight to afford the 3-hydroxy-3-cyclobutene-1,2-diones **6a,b,c**. Further hydrolysis with 6 N HCl in refluxing acetic acid[9] yielded the desired 3-(aminoalkyl)-4-hydroxy-3-cyclobutene-1,2-diones. Separation of the amino acids from phthalic acid was achieved by suspending the evaporated reaction mixture in water and filtering off the phthalic acid. The zwitterions were generated by treating the hydrochloride salts of **1b** and **1c** with propylene oxide in ethanol. Compound **1a** was too acidic to be protonated, even by hydrochloric acid. Most likely the difficulty in isolating these polar materials from phthalic acid led to the low yields in the last step of **1a** and **1b**.

The glycine derivative **1a** was more efficiently synthesized by an alternate route (Scheme 2),[10] based on the addition of alkyllithiums to dialkoxycyclobutenediones.[11] The lithium salt of methyl isocyanide (**7**) was generated with *sec*-butyllithium in tetrahydrofuran at −78 °C, and it was added to 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**8**). Upon quenching with acetic acid and purification by flash chromatography, the 1,2-addition adduct **9** was isolated. Compound **9** was hydrolyzed with 6 N HCl at room temperature overnight to afford **1a** in 82% yield. This material was identical to that prepared above when examined by CHN analysis, and ^{1}H NMR and IR spectroscopy.

Compounds **1a–c** were tested in the strychnine-insensitive [^{3}H]glycine binding assay as described in the literature.[3] All compounds were found to be inactive at 100 μM, whereas the known glycine antagonist 7-chlorokynurenic acid exhibited an IC_{50} of 0.35 μM. Although these results were disappointing, the tetrazole glycine mimic **10** was also inactive at the glycine receptor;[12] this is probably due to their larger size. Therefore the glycine receptor is a fairly demanding target for carboxylic acid bioisosteres, and this result should not discourage the the wider application of the 3-hydroxy-3-cylcobutene-1,2-dione group as a carboxylic bioisostere.



1a



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Conclusion

Chemistry has been introduced which allows efficient synthesis of biologically important amino acids substi-

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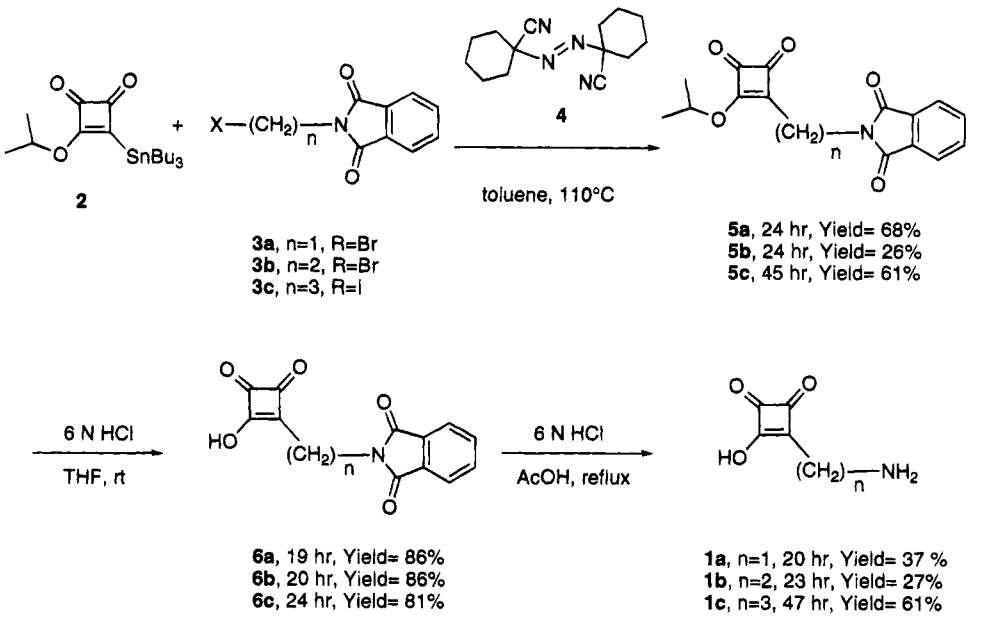
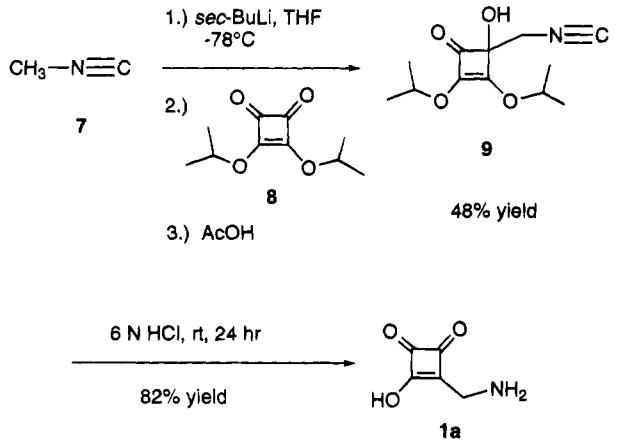
Scheme 1



Scheme 2



tuted with 3-hydroxy-3-cyclobutene-1,2-dione. This should contribute to further exploitation of the 3-hydroxy-3-cyclobutene-1,2-dione group as a carboxylic acid bioisostere in medicinal chemistry. The cyclobutenedione group has already proven to be a versatile building block for bioisostere construction[13,14] and it is expected that further applications will develop.

Experimental Section

Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR spectra were obtained at either 200 or 400 MHz on a Varian XL-200 or Bruker AM-400 spectrometer, respectively. Mass spectra were measured on either a Finnigan 8230 or Hewlett-Packard 5995A mass spectrometer. Elemental analyses were obtained on a Control Equipment 240-XA elemental analyzer. Flash chromatography refers to the technique described by Still.[15] The diameter of the column used is noted, but the height of silica gel 60 (400-230 mesh) was 20 cm in all cases.

3-Isopropoxy-4-(3-phthalimidoprop-1-yl)-3-cyclobutene-1,2-dione (5c). A solution of **3c** (2.80 g, 8.88 mmol)[16] and **2** (7.82 g, 18.2 mmol) in anhydrous toluene (15 mL) under nitrogen was treated with **4** (216 mg, 0.86 mmol) and brought to boiling. Additional initiator was added at 5 h (444 mg), 22 h (300 mg), and 30 h (372 mg). After 45 h, the reaction mixture was evaporated, dissolved in acetonitrile (100 mL), and washed with hexane (4 × 50 mL) with stirring (15 min) to remove tributyltin iodide. The acetonitrile layer was evaporated, dissolved in ethyl acetate, treated with silica gel, and evaporated. The solid was deposited on an eluted silica gel column (7.5 cm diameter). Gradient elution with 10–30% ethyl acetate in petroleum ether afforded **5c** (1.78 g, 61%, mp 135–137 °C): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.88–7.71 (m, 4H), 5.42 (hept, J = 6 Hz, 1H), 3.78 (t, J = 7 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.12 (p, J = 7.5 Hz, 2H), 1.46 (d, J = 6 Hz, 6H); IR (KBr, cm^{-1}) 1790, 1765, 1750, 1700, 1590, 1390, 1100, 1020, 710. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.66; H, 5.37; N, 4.34.

3-Hydroxy-4-(3-phthalimidoprop-1-yl)-3-cyclobutene-1,2-dione (6c). A solution of **5c** (2.02 g, 6.17 mmol) in tetrahydorfuran (120 mL) was treated with 6 N hydrochloric acid solution (29 mL) at rt. After 24 h the reaction mixture was concentrated in vacuo, treated with water, and evacuated again (2 × 50 mL). The resulting solid was recrystallized from chloroform in hexane (60 mL) to afford **6c** (1.44 g, 81%, mp 164–166 °C dec): ^{1}H NMR (DMSO, 400 MHz) δ 7.87–7.81 (m, 4H), 3.63 (t, J = 7 Hz, 2H), 2.52 (t, J = 7.5 Hz, 2H), 1.93 (p, J = 7 Hz, 2H); MS (DCI+) 286 (100, M + H), 148 (20). Anal. Calcd for $C_{15}H_{11}NO_5 \cdot 0.1H_2O$: C, 62.76; H, 3.93; N, 4.88. Found: C, 62.57; H, 3.77; N, 4.90.

3-(3-Aminoprop-1-yl)-4-hydroxy-3-cyclobutene-1,2-dione (1c). The phthalimide group of **6c** (490 mg, 1.7 mmol) was cleaved in acetic acid (20 mL) and 6 N hydrochloric acid solution (20 mL) at reflux for 47 h under nitrogen. The reaction mixture was evaporated, treated with water (50 mL), filtered, and evaporated. The crude product was dissolved in water, evaporated, dissolved in ethanol (5 mL), cooled to 0 °C, and treated with propylene oxide (0.40 mL, 5.7 mmol). After 1 h at rt, ethyl acetate was added (10 mL) and an ice bath was applied. The filtered solid was recrystallized from methanol in ethyl acetate (20 mL) to afford **1c** (162 mg, 61%, mp 165–180 °C dec) as a beige solid: ^{1}H NMR (DMSO, 400 MHz): δ 7.72 (br s, NH_3), 2.87 (br t, J = 7 Hz, 2H), 2.42 (t, J = 7 Hz, 2H), 1.81 (p, J = 7 Hz, 2H); IR (KBr, cm^{-1}) 1780, 1700, 1550. Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.86; H, 5.70; N, 8.75.

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3-Isopropoxy-4-(2-phthalimidoethyl)-3-cyclobutene-1,2-dione (5b): yield 26% from **3b**; mp 88–92 °C; ^{1}H NMR (DMSO, 400 MHz) δ 7.90–7.83 (m, 4H), 5.17 (hept, J = 6 Hz, 1H), 3.85 (t, J = 6.5 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 1.18 (d, J = 6 Hz, 6H); IR (KBr, cm^{-1}) 1800, 1770, 1750, 1710, 1590, 1430, 1390, 1095, 710; MS (+FAB) 314 (24, M + H), 272 (100), 148 (44). Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.96; H, 4.86; N, 4.64.

3-Hydroxy-4-(2-phthalimidoethyl)-3-cyclobutene-1,2-dione (6b): yield 86% from **5b**; mp 93–95 °C; ^{1}H NMR (DMSO, 400 MHz) δ 7.88–7.81 (m, 4H), 3.82 (t, J = 7 Hz, 2H), 2.84 (t, J = 7 Hz, 2H); IR (KBr, cm^{-1}) 1805, 1770, 1705, 1400, 1100, 710; MS (+FAB): 272 (M + H, 100), 217 (65), 160 (45). Anal. Calcd for $C_{14}H_9NO_5 \cdot 0.05H_2O$: C, 61.79; H, 3.37; N, 5.15. Found: C, 61.47; H, 3.43; N, 5.46.

3-(2-Aminoethyl)-4-hydroxy-3-cyclobutene-1,2-dione (1b): yield 27% from **6b**; mp 145–150 °C dec; ^{1}H NMR (DMSO, 400 MHz) δ 8.1 (br s, NH_3), 3.06 (t, J = 6 Hz, 2H), 2.68 (t, J = 6 Hz, 2H); IR (KBr, cm^{-1}) 3400, 1775, 1700, 1600, 1085. Anal. Calcd for $C_6H_7NO_3 \cdot 0.15H_2O$: C, 50.11; H, 5.12; N, 9.74. Found: C, 50.01; H, 4.76; N, 9.73.

3-Isopropoxy-4-(phthalimidomethyl)-3-cyclobutene-1,2-dione (5a): yield 68% from **3a**; mp 95 °C; ^{1}H NMR (DMSO, 400 MHz) δ 7.95–7.88 (m, 4H), 5.21 (hept, J = 6 Hz, 1H), 4.83 (s, 2H), 1.26 (d, J = 6 Hz, 6H); IR (KBr, cm^{-1}) 1800, 1720, 1590, 1400, 1310, 1090, 720; MS (EI) 299 (M$^+$, 8%), 271 (15), 228 (20), 160 (100). Anal. Calcd for $C_{16}H_{13}NO_5 \cdot 0.5H_2O$: C, 62.34; H, 4.58; N, 4.54. Found: C, 62.27; H, 4.65; N, 4.85.

3-Hydroxy-4-(phthalimidomethyl)-3-cyclobutene-1,2-dione (6a): yield 86% from **5a**; mp 135 °C dec; ^{1}H NMR (DMSO, 400 MHz) δ 7.91–7.84 (m, 4H), 4.63 (s, 2H); IR (KBr, cm^{-1}) 1805, 1720, 1600, 1400, 1300, 1180, 1020, 930, 710; MS (PB/EI): 258 (M + H, 7), 229 (23), 173 (62), 161 (100), 104 (86), 76 (97). Anal. Calcd for $C_{13}H_7NO_5 \cdot 1.5H_2O$: C, 54.94; H, 3.55; N, 4.93. Found: C, 55.13; H, 3.17; N, 5.41.

3-(Aminomethyl)-4-hydroxy-3-cyclobutene-1,2-dione (1a): yield 37% from **6a**; mp 124–168 °C dec; ^{1}H NMR (DMSO, 400 MHz) δ 8.04 (br s, NH_3), 3.77 (q, J = 5.5 Hz, 2H); IR (KBr, cm^{-1}) 1770, 1720, 1550, 1135, 1020; MS (DEI) 126 (M − H). Anal. Calcd for $C_5H_5NO_3 \cdot 0.1H_2O$): C, 46.59; H, 4.07; N, 10.87. Found: C, 46.34; H, 3.92; N, 10.93.

Preparation of 9. A solution of methyl isocyanide[17] (**7**, 1.80 mL, 29.9 mmol) in anhydrous tetrahydrofuran (26 mL) under nitrogen at −78 °C was treated dropwise with 1.3 M *sec*-butylithium in cyclohexane (23 mL, 29.9 mmol). After 45 min, the lithiated methyl isocycanide was cannulated into a solution of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**8**, 5.93 g, 29.9 mmol) in tetrahydrofuran (40 mL) at −78 °C. After 1.5 h the reaction mixture was quenched with acetic acid (1.7 mL, 30 mmol), warmed to rt, treated with water (65 mL), extracted with dichloromethane (3 × 50 mL), and dried with potassium carbonate. The evaporated residue was purified by flash chromatography (6 cm diameter, gradient elution with 10–15% ethyl acetate in petroleum ether) to afford the 1,2-addition product **9** (3.45 g, 48%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.97 (hept, J = 6.2 Hz, 1H), 4.91 (hept, J = 6.2 Hz, 1H), 4.65 (br s, 1H), 3.80 (d, J = 15.4 Hz, 1H), 3.71 (d, J = 15.4 Hz, 1H), 1.45 (d, J = 6.2 Hz, 3H), 1.44 (d, J = 6.2 Hz, 3H), 1.30 (app d, J = 6.8 Hz, 6H); IR (CH_2Cl_2, cm^{-1}) 3570, 3370, 2893, 2940, 2880, 2160, 1772, 1623, 1410, 1390, 1324, 1100.

3-(Aminomethyl)-4-hydroxy-3-cyclobutene-1,2-dione (1a) from 9. A solution of **9** (3.45 g, 14.4 mmol) in 6 N hydrochloric acid solution was stirred for 24 h. The solvent was removed, and the reaction mixture was treated with water and evaporated (2×). The residue was stirred in acetone (50 mL) for 7 h, and a light brown solid was filtered, washed with acetone, and dried overnight under vacuum to yield **1a** (1.51 g, 82%), identical to that prepared above as shown by ^{1}H NMR, IR, and CHN analyses.

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