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Synthesis of Alkyl Substituted Cyclobutenediones by Free Radical Chemistry. Carbon for Nitrogen Replacement in the α-Amino Acid Bioisostere -- 3,4-Diamino-3-cyclobutene-1,2-dione.

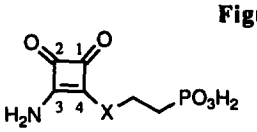
William A. Kinney

Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543-8000

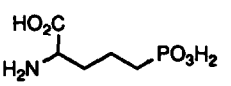
Abstract: A novel free radical method for the synthesis of alkyl substituted cyclobutenediones was demonstrated, allowing for incorporation of a variety of functionalities. The synthesis of an analog of NMDA antagonist 1 was thereby facilitated.

The novel NMDA antagonist **1** was recently described (IC_{50}=0.47μM in [^{3}H]-CPP binding assay),[1] which contains the 3,4-diamino-3-cyclobutene-1,2-dione group as a unique α-amino acid bioisostere. This group has a dipole, represented by the contributing resonance forms below (Figure), making it an electronic mimic of the α-ammonium carboxylate contained in 2-amino-5-phosphonopentanoic acid **3** at physiological pH. While the 3-amino group of **1** appeared necessary for correspondence to the 2-amino group of **3**, the necessity of the 4-amino group for donation of its lone pair electrons to the opposite 2-oxo carbonyl within **1** was suspect. Target **2**, which contains a carbon atom in place of the 4-amino group, was considered the appropriate SAR probe; retrosynthetic analysis of **2** led to **6** (Scheme) as the required intermediate.

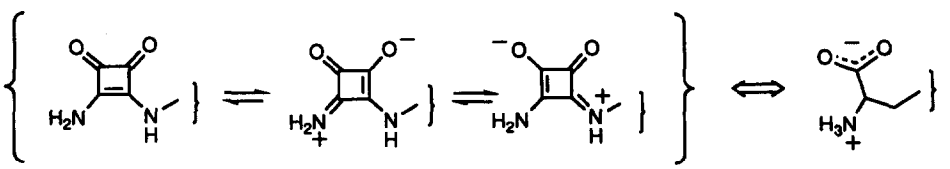
Figure



X = NH (**1**), CH_2 (**2**)



3

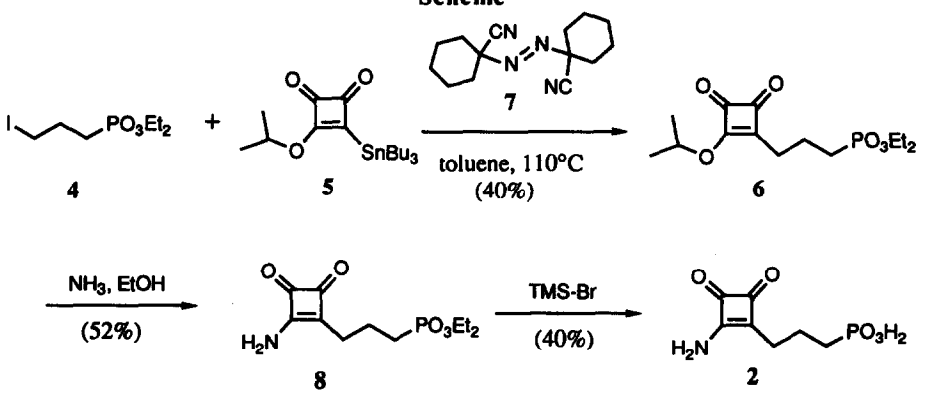


Mono- and dialkyl-substituted cylclobutenediones have received much attention by virtue of their importance as synthetic precursors.[2] Recent procedures to prepare monosubstituted derivatives involve organolithium[3,4] or Grignard[5] addition to 3,4-dialkoxycylcobutene-1,2-diones, and then either hydrochloric

acid or trifluoroacetic acid anhydride rearrangement to afford 3-alkoxy-4-alkylcylcobutene-1,2-diones. The related reaction of zinc-copper organometallics with 3,4-dichlorocyclobutene-1,2-dione was just published,[6] which allows for the incorporation of a single alkyl group containing sensitive functionalities, such as carboxylic esters in moderate yield (52%).

An alternative free radical approach was developed in this lab, which is compatible with the presence of the diethoxyphosphinyl group required for the synthesis of **6**, as well as other functionalities. Liebeskind's tri-*n*-butyltincyclobutenedione reagent **5** (Scheme) has been utilized for palladium-catalyzed Stille cross couplings with vinyl and aryl iodides.[7] However, for unactivated alkyl halide coupling partners, free radical additions to **5** were considered more useful; such additions to analogous acyclic vinyltin systems has been demonstrated by Baldwin.[8]

Scheme

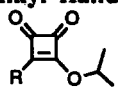


The alkyl radical was generated from **4** with azobiscylclohexylnitrile **7** as the initiator[9] (110 °C, 24 h) in the presence of **5**. Addition of the alkyl radical occurred, followed by the elimination of trialkyltin radical, to afford the desired adduct **6** in moderate yield. Reaction of **6** with ammonia in ethanol afforded the phosphonate ester **8**, which was subsequently deprotected with bromotrimethylsilane to deliver **2** (yields unoptimized). When **2** was evaluated for NMDA receptor affinity by its ability to displace the [^{3}H]-CPP ligand,[1] it was found to be inactive at 10 μM, demonstrating the importance of the 4-amino group in **1**.

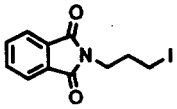
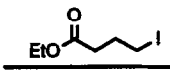
The generality of this free radical method was then pursued by examining the reaction of other alkyl halides (Table) to yield 4-alkylcyclobutene-1,2-diones **9a-e**.[10] In all cases, two equivalents of reagent **5** (1.2 M **5** in toluene) were utilized and approximately 0.1 equivalents of initiator was introduced every twelve hours. Originally, initiation was achieved with azobisisobutyronitrile (AIBN, 85 °C),[11] but the reactions were slow requiring at least 48 h for disappearance of starting alkyl halide. When initiator **7** was substituted for AIBN (110 °C), the reactions were complete within 24 h (**6**, **9c** and **9e**). The yields were good in the case of primary iodides, but either primary bromides (**9a**) or secondary iodides (**9c**) were less useful substrates. In the case of **9d** and **9e**, as with **6**, functional groups were introduced which would be incompatible with the organolithium or Grignard approaches. The more recent zinc-copper organometallic method of Knochel also provides entry into functionalized 4-alkylcyclobutene-1,2-dione systems.

In summary, this novel free radical procedure provides an additional method for incorporation of functionalized alkyl groups into the cyclobutenedione moiety, which was useful in the synthesis of a critical NMDA antagonist analog **2**.

Table. Reaction of Alkyl Halides with Reagent 5 to Yield 9.



9 a-e

Alkyl Halide	Catalyst	Mole Equiv.	Rxn Time (h)	Rxn Temp (°C)	Product	Yield (%)
	AIBN	0.48	22	95	**9a**	7
	AIBN	0.63	46	85	**b**	52
	7	0.19	22	110	**c**	21
	7	0.43	46	110	**d**	39
	7	0.25	22	110	**e**	56

[3-[2-(1-Methylethoxy)-3,4-dioxocyclobut-1-enyl]propyl]phophonic acid diethyl ester (6). Diethyl 3-iodopropylphosphonate[12] (367 mg, 1.20 mmol), **5** (1.00 g, 2.33 mmol), and initiator **7** (30 mg, 0.12 mmol) were combined, evacuated, and blanketed with nitrogen. Anhydrous toluene (2 mL) was added and an oil bath (110°C) was applied for 24 h; additional **7** (45 mg, 0.18 mmol) was added through the condenser at 7 h. The reaction mixture was evaporated and partitioned between acetonitrile (50 mL) and hexane (30 mL) with vigorous stirring for 20 min. The layers were separated and the acetonitrile layer was processed with three additional hexane washes to remove tri-*n*-butyltin iodide.[13] The solution was evaporated onto silica gel, placed on an eluted column of silica gel (4 cm diameter), and purified by flash chromatography (gradient elution with 1-2% methanol in dichloromethane) to afford **6** as a yellow oil (155 mg, 40%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.40 (hept, J=6Hz, 1H), 4.16-4.04 (m, 4H), 2.70 (t, J=7.5Hz, 2H), 2.03-1.94 (m, 2H), 1.84-1.75 (m, 2H), 1.44 (d, J=6Hz, 6H), 1.31 (t, J=7Hz, 3H); IR (neat, cm^{-1}): 3000, 1790, 1750, 1590, 1390, 1240, 1095, 1020, 955; MS (+FAB): 319 (MH^+, 60), 277 (100).

[3-[2-Amino-3,4-dioxocyclobut-1-enyl]propyl]phophonic acid (2). Compound **6** (121 mg, 0.38 mmol) was dissolved in ammonia saturated ethanol (10 mL) and after 30 min the reaction mixture was concentrated *in vacuo*. The crude product was applied in dichloromethane to a silica gel column (3 cm diameter) and eluted (gradient with 2.5 - 5% methanol in dichloromethane) to yield **8** (54 mg, 52%) as a pale yellow oil.[14] A solution of **8** (150 mg, 0.54 mmol) in anhydrous 1,2-dichloroethane (5.5 mL) under nitrogen was treated with bromotrimethylsilane (0.54 mL, 4.1 mmol) and heated to reflux for 15 min. The reaction mixture was concentrated *in vacuo*, dissolved in water (20 mL), washed with diethyl ether (2 x 10 mL), and concentrated to

afford an oil, which was crystallized[15] from methanol in ethyl acetate (5 mL) to yield **2** as a beige solid (48 mg, 40%, mp 180-183 °C dec). ^{1}H NMR (DMSO, 400 MHz): δ 8.60 (br s, NH), 8.50 (br s, NH), 2.59 (t, J=7Hz, 2H), 1.83-1.72 (m, 2H), 1.59-1.50 (m, 2H); IR (KBr, cm^{-1}): 3370, 3100, 1790, 1730, 1650, 1560, 1240, 1090, 1000, 950; MS (-FAB): 218 (M-H); Anal. ($C_7H_{10}NO_5P$) C, H, N.

Acknowledgments

I would like to credit Prof. Dennis Curran for many helpful discussions on free radical chemistry. Also, thanks go to Dianne Kowal for [^{3}H]-CPP binding data.

References and Notes

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2. See footnote 2 contained in reference 7 below.
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10. The ^{1}H NMR spectrum for **9a** matched the literature spectrum [Ref. 3, error 1.46 (d, J=6Hz, 6H)]. Spectral data for compounds **9b-e** below:

    9b ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.41 (hept, J=6 Hz, 1H), 2.59 (t, J=8Hz, 2H), 1.8-1.6 (m, 2H), 1.46 (d, J=6Hz, 6H), 1.4-1.3 (m, 4H), 0.90 (t, J=7Hz, 3H); IR (neat, cm^{-1}): 1790, 1750, 1590, 1390, 1095; MS (EI): 210 (M$^+$, 2), 182 (12), 139 (37), 71 (100).

    9c ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.42 (hept, J=6Hz, 1H), 2.76 (t of t, J=10 and 2 Hz, 1H), 2.0-1.2 (m, 10H), 1.44 (d, J=6Hz, 6H); IR (neat, cm^{-1}): 2940, 1790, 1750, 1590, 1390, 1340, 1100; Anal. ($C_{13}H_{18}O_3$) C, H.

    9d ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.88-7.71 (m, 4H), 5.42 (hept, J=6Hz, 1H), 3.78 (t, J=7Hz, 2H), 2.66 (t, J=7.5Hz, 2H), 2.12 (p, J=7.5Hz, 2H), 1.46 (d, J=6Hz, 6H); IR (KBr, cm^{-1}): 1790, 1765, 1750, 1700, 1590, 1390, 1100, 1020, 710; Anal. ($C_{18}H_{17}NO_5$) C, H, N.

    9e ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.42 (hept, J=6Hz, 1H), 4.14 (q, J=7Hz, 2H), 2.67 (t, J=7.5Hz, 2H), 2.39 (t, J=7Hz, 2H), 2.03 (p, J=7Hz, 2H), 1.46 (d, J=6Hz, 6H), 1.26 (t, J=7Hz, 3H); IR (neat, cm^{-1}): 1790, 1750, 1730, 1590, 1390, 1095; Anal. ($C_{13}H_{18}O_5$) C, H.
11. Both AIBN and **7** available from K and K Laboratories.
12. C. F. Bigge, S. J. Hays, P. M. Novak, J. T. Drummond, G. Johnson, and T. P. Bobovski, *Tetrahedron Letters* **1989**, *30*, 5193.
13. For less polar examples (e.g. **9c**), only two hexane washes were sufficient. Or the alternative DBU procedure was utilized (e.g. **9a,b**): D. P. Curran and C-T. Chang, *J. Org. Chem.* **1989**, *54*, 3140.
14. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.5 (br s, NH), 5.9 (br s, NH), 4.2-4.0 (m, 4H), 2.89 (t, J=6.5Hz, 2H), 2.2-1.9 (m, 2H), 1.85-1.65 (m, 2H), 1.36 (t, J=7Hz, 6H); IR (neat, cm^{-1}) 3330, 3130, 3000, 1790, 1730, 1650, 1580, 1450, 1420, 1220, 1030, 970; MS (EI): 275 (M$^+$, 35), 247 (44), 219 (74), 166 (100), 138 (92).
15. A black solid, which precipitated the first several times, was discarded.

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