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Kinetic stabilization of the o-quinoidal 3,4-benzotroponone system

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Kinetic stabilization of the o-quinoidal 3,4-benzotroponone system was investigated. The parent 3,4-benzotroponone 1 undergoes rapid [π8 + π10] dimerization in fluid solution even at −78 °C while triptycene-fused derivative 5 having a tert-butyl group at the C(6) position of the tropone moiety was found to be stable indefinitely under similar conditions. The relative importance of the tropone moiety and the tert-butyl group in 5 for the kinetic stabilization was evaluated.

Introduction

3,4-Benzotropones, in which the benzo component is fused to the tropone ring in a manner to form an o-quinoidal structure, have long been a subject of theoretical1 and experimental2,3 interest. We have previously reported4 the generation of the parent 3,4-benzotroponone 1 using the electrocyclic ring-opening reaction of the corresponding benzo-cyclobutene isomer 2. UV-vis and IR spectroscopic studies have revealed that 1 is electronically significantly polarized in the ground state, consistent with a substantial contribution of polarized resonance structure 1b. Despite the unique electronic structure, however, the thermal instability of 1 has thwarted the exploration of its physical and chemical properties; 1 is persistent only under matrix isolation conditions at low temperature and is rapidly consumed in fluid solution even at −78 °C. We were interested in investigating the kinetic stabilization of 1 to gain a more detailed understanding of this system. The lability of o-quinoidal 1 arises from its high propensity to undergo dimerization to form dimers 3 and 4. This tendency suggests that the system may be kinetically stabilized, to some extent at least, by introducing sterically demanding substituents that specifically shield the reaction sites, and we designed derivatives 5–8. Herein we report the results of synthetic investigation of 5–8 aimed at generating the kinetically stabilized derivatives of 1.

Results and discussion

A major path of the thermal decomposition of 1 is a kinetically controlled [π8 + π10] dimerization at the 2,5- and 2,7-positions to form 3 and 4.5 To prevent such dimerization, triptycene-fused derivative 5 having a tert-butyl group at the C(6) position was designed as an initial target molecule. Related compounds 6 and 7 were also investigated to evaluate the relative importance of the tert-butyl group and the fused triptycene moiety for the kinetic stabilization of this system.

On the basis of our previous successful generation of 1 from the corresponding benzocyclobutene valence isomer 2, we envisaged 13 as a promising precursor for 5, and 13 was prepared as outlined in Scheme 1. Thus, addition of benzyl to 9 afforded triptycene derivative 10 in 73% yield. Bromination of 10 followed by dehydrobromination and deprotection afforded enone 12 in 47% yield. 1,2-Addition of tert-butyl lithium to 12 followed by PCC oxidation produced 13 in 61% yield. On the other hand, 1,2-addition of tert-butyl lithium to 2 followed by PCC oxidation produced 14 in 58% yield (Scheme 2).

The photochemical generation of 5 from 13 was examined under matrix isolation conditions at low temperature and the reaction was monitored by UV-vis spectroscopy. When a degassed EPA (a 5:5:2 mixture of ether, isopentane, and ethanol) solution of 13 in a Pyrex tube was frozen at liquid nitrogen temperature (−196 °C) and irradiated with a high-pressure mercury lamp, a new absorption extending to long-wavelength region with λmax around 450 nm was observed (Fig. 1). This newly developed absorption is almost superimposed on that reported4 for 1 with λmax at 353, 372, 392, 458, 482 (sh), 506 (sh) and 518 (sh) nm. Similarly, irradiation of 12 or 14 in an EPA glass at −196 °C led to the development of a new absorption characteristic of the 3,4-benzotroponone system (see experimental section). Thus, we concluded that 3,4-benzotroponone derivatives 5, 6 and 7 were generated photochemically from 13, 12 and 14, respectively. The generated orange species 5–7 were stable in the frozen EPA glass, but were consumed smoothly in the fluid EPA solution at 0 °C. The decay of the absorption followed second-order kinetics (Fig. 2), so that dimer formation should be still a dominant pathway for their thermal decomposition. The rate constants (Table 1) for the dimerization of 5, 6 and 7 in EPA at 0 °C were determined to be 30 ± 6 M−1 s−1, 166 ± 33 M−1 s−1 and 60 ± 12 M−1 s−1, respectively. These observations demonstrate that
of 18 with 1-(ethynylsulfonyl)-4-methylbenzene followed by dehydrogenation gave 19 in 83% yield. Bromination of 19 followed by dehydrobromination and deprotection afforded 21 in 52% yield. 1,2-Addition of tert-butyllithium to 21 followed by PCC oxidation produced 22 in 32% yield.

The photochemical generation of 8 from 22 was examined as described for 5–7. However, unexpectedly, when a degassed EPA solution of 22 in a Pyrex tube was irradiated with a high-pressure mercury lamp at −196 °C, development of no absorption extending to long-wavelength region characteristic of the 3,4-benzotropane system was observed, even after prolonged irradiation. Molecular modeling suggests that 8 would be distorted from its ideal planar structure due to the steric repulsion between the tert-butyl group at the C(2) position and the hydrogen atom at the peri-position (Scheme 4). To relieve the steric repulsion, 8 may undergo, if it is generated, rapid pericyclic ring-closing photochemical reaction to form norcaradiene derivative 23. A similar photochemical transformation has been reported for related compounds.\(^{2,6c}\)

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**Scheme 1**

(a) Anthranilic acid, isopentyl nitrite, refluxing DME, 7 h, 73%; (b) PyHBr\(_3\), dichloromethane, room temperature, 5 h, then t-BuOK, 18-crown-6, THF, room temperature, 20 h, 52%; (c) aqueous HCl, THF, 50 °C, 3 h, 90%; (d) t-BuLi, THF, −78 °C, 1 h, then PCC, dichloromethane, room temperature, 40 h, 61%.

**Scheme 2**

(a) t-BuLi, THF, −78 °C, 1 h, then PCC, dichloromethane, room temperature, 63 h, 58%.

the tert-butyl group is more effective than the triptycene moiety for the kinetic stabilization of this system. It is interesting to point out that 5 is stable indefinitely in an EPA solution at −78 °C; whereas parent 1 undergoes dimerization with the rate constant of 12 ± 3 M\(^{-1}\) s\(^{-1}\) under the same conditions. Unfortunately, however, attempted characterization of 5 by \(^1\)H NMR spectroscopy at low temperature failed, owing to the severe internal filtering of 13 by generating 5 which resulted in limited photochemical conversion of 13.

**Table 1** Kinetic stabilities of the 3,4-benzotropones in EPA

<table>
<thead>
<tr>
<th>Compound</th>
<th>Temp/°C</th>
<th>(k/\text{M}^{-1}\text{s}^{-1})</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−78</td>
<td>12 ± 3</td>
<td>reference 4</td>
</tr>
<tr>
<td>5</td>
<td>−78</td>
<td>stable</td>
<td>this study</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>30 ± 6</td>
<td>this study</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>166 ± 33</td>
<td>this study</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>60 ± 12</td>
<td>this study</td>
</tr>
</tbody>
</table>
The mixture was cooled to room temperature, diluted with chloroform (100 mL), and the mixture was heated at 50 °C for 3 h. The mixture was extracted with ethyl acetate (2 × 100 mL). The extracts were combined, washed successively with water (2 × 500 mL), 5% aqueous HCl (2 × 500 mL), 10% aqueous NaHCO₃ (2 × 500 mL) and brine (3 × 500 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/hexane (1:9) to give 10 (1.33 g, 73%); mp 237–243 °C (ether); (Found 376.1469, C₁₇H₁₇O₂ requires 376.1463); νmax (KBr)/cm⁻¹ 1364, 1142, 970, δ₁H (75 MHz, CDCl₃) 1.52–1.88 (m, 4 H), 3.74 (d, J = 3.8 Hz, 1 H), 3.96–4.15 (m, 4 H), 4.24 (dd, J = 3.8 and 2.5 Hz, 1 H), 5.34 (s, 1 H), 5.37 (s, 1 H), 5.50 (d, J = 5.5 Hz, 1 H), 6.30 (dd, J = 5.5 and 2.5 Hz, 1 H), 6.92–6.97 (m, 4 H), 7.11 (s, 1 H), 7.24 (s, 1 H) and 7.31–7.35 (m, 4 H); δ₁C (75 MHz, CDCl₃) 25.61, 31.92, 45.30, 51.64, 54.55, 54.65, 63.97, 65.10, 65.11, 115.00, 117.97, 119.02, 122.77, 123.33, 123.40, 123.47, 123.83, 124.98, 125.01, 125.03, 140.29, 143.38, 144.79, 145.25, 145.27, 145.32, 145.55 and 147.05; m/z (FD) 378 (M⁺, 100%).

5.7-12,3'-3'-9',10'-Dihydro-9',10'-benzo-endo-bicyclo[3.2.0]hepta-6,2-dien-2-one ethylene acetal (11). To a solution of 10 (1.33 g, 3.51 mmol) in dichloromethane (80 mL) was added pyridinium tribromide (1.13 g, 3.51 mmol) in portions, and the mixture was stirred at room temperature for 5 h and then poured into 10% aqueous Na₂SO₄ (100 mL). The organic layer was separated, washed with brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was dissolved in 100 mL of dry THF and used for the next reaction without further purification. To the THF solution was added potassium tert-butoxide (3.39 g, 30.3 mmol) and 10% aqueous HCl (2 × 500 mL), 10% aqueous NaHCO₃ (2 × 500 mL) and brine (3 × 500 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate (2 × 100 mL). The extracts were combined, washed with brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was recrystallized from ethyl acetate/hexane (1:9) to give 11 (0.68 g, 52%); mp 237–239 °C (ether); (Found 376.1469, C₁₇H₁₇O₂ requires 376.1463); νmax (KBr)/cm⁻¹ 1364, 1142, 970, δ₁H (75 MHz, CDCl₃) 25.61, 31.92, 45.30, 51.64, 54.55, 54.65, 63.97, 65.10, 65.11, 115.00, 117.97, 119.02, 122.77, 123.33, 123.40, 123.47, 123.83, 124.98, 125.01, 125.03, 140.29, 143.38, 144.79, 145.25, 145.27, 145.32, 145.55 and 147.05; m/z (FD) 378 (M⁺, 100%).
brine (50 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/hexane (1:9) to give 12 (0.50 g, 90%); mp 256–257 °C (ether); (Found 332.1196, C₁₄H₁₄O requires 332.1191); v max (KBr/cm⁻¹) 1696; δ₁₇ (300 MHz; CDCl₃) 3.97 (d, J = 3.0 Hz, 1 H), 4.45 (d, J = 3.0 and 2.6 Hz, 1 H), 5.38 (s, 1 H), 5.39 (s, 1 H), 5.95 (d, J = 5.5 Hz, 1 H), 6.95–7.00 (m, 4 H), 7.21 (s, 1 H), 7.26 (s, 1 H), 7.32–7.40 (m, 4 H) and 7.70 (d, J = 5.5 and 2.6 Hz, 1 H); δ₁₅ (75 MHz, CDCl₃) 49.87, 51.83, 54.17, 54.25, 118.39, 119.54, 123.22, 123.25, 123.37, 123.41, 124.96, 123.98, 125.02, 125.07, 133.44, 137.95, 137.97, 143.22, 144.65, 144.71, 144.74, 147.49, 150.20, 161.53 and 205.06; m/z (FD) 541 (M⁺, 100%).

5-tert-Butyl-6,7-bis(chloromethyl)bicyclo[3.2.0]heptan-3-one (17). A mixture of 16 (0.87 g, 3.3 mmol), ethylene glycol (0.41 g, 6.6 mmol), and p-toluene sulfonic acid monohydrate (62 mg, 0.3 mmol) in benzene (90 mL) was heated under reflux for 2 h while water was removed with a Dean–Stark trap. The mixture was cooled, diluted with ether (100 mL), washed successively with aqueous NaHCO₃ (80 mL), water (100 mL), and brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:9) to give 17 (0.93 g, 91%) as a mixture of stereoisomers; (Found 306.1142, C₁₄H₁₂O₂Cl requires 306.1153); v max (KBr/cm⁻¹) 1100; δ₁₇ (300 MHz; CDCl₃) 0.91 (s, 9 H), 1.49–1.56 (m, 1 H), 1.82–1.93 (m, 2 H), 2.03–2.11 (m, 3 H), 2.46–2.49 (m, 1 H), 3.46–3.72 (m, 4 H) and 3.88–3.95 (m, 4 H); m/z (FD) 310 (M⁺ + 4, 14.4%), 308 (M⁺ + 2, 66.2%) and 306 (M⁺, 100%).

5-tert-Butyl-6,7-bis(methylene)bicyclo[3.2.0]heptan-2-one (18). To a solution of 17 (358 mg, 1.17 mmol) in dry THF (50 mL) was added potassium tert-butoxide (392 mg, 3.5 mmol) and the mixture was stirred at room temperature under argon for 3 h and then evaporated. Water (100 mL) was added to the residue and the mixture was extracted with ether (3 × 70 mL). The extracts were combined, washed with brine (100 mL), dried (Na₂SO₄) and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:9) to give 18 (260 mg, 95%) as a colorless oil; (Found 234.1608, C₁₄H₁₀O₂ requires 234.1620); v max (KBr/cm⁻¹) 1098; δ₁₇ (300 MHz; CDCl₃) 0.94 (s, 9 H), 1.80–2.20 (m, 4 H), 2.77 (s, 1 H), 7.26 (s, 1 H) and 7.33–7.39 (m, 4 H); δ₁₅ (75 MHz, CDCl₃) 29.08, 35.26, 49.37, 53.89, 54.33, 54.50, 119.31, 119.59, 123.39, 123.52, 123.58, 123.64, 124.17, 124.25, 129.27, 131.15, 138.82, 143.87, 144.90, 143.93, 145.00, 145.05, 145.07, 145.09, 145.32, 147.28 and 204.81; m/z (FD) 386 (M⁺, 100%).

5-tert-Butyl-6,7-bis(benzyloxy)bicyclo[3.2.0]heptan-2-one (19). A solution of 18 (0.48 g, 2.1 mmol) and 1-(ethylen-sulfonyl)-4-methylbenzenoë (0.37 g, 2.0 mmol) in benzene (5 mL) was refluxed for 5 h. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), washed with water (50 mL), dried with Na₂SO₄, and concentrated. The residue was added DMSO (75 mL), water (75 mL), Na₂SO₄ (0.95 g, 5.4 mmol) and NaHCO₃ (1.0 g, 11.9 mmol) and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with water (100 mL) and extracted with ether (4 × 100 mL). The extracts were combined, washed successively with aqueous water (2 × 100 mL) and brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:9) to give 19 (0.43 g, 83%); mp 167.5–168 °C (hexane); (Found 258.1612, C₁₄H₁₀O₂ requires 258.1620); v max (KBr/cm⁻¹) 1090; δ₁₇ (300 MHz; CDCl₃) 0.91 (s, 9 H), 1.58–1.70 (m, 2 H), 1.94–2.05 (m, 2 H), 3.33 (s, 1 H), 3.90–4.04 (m, 4 H), 7.03–7.06 (m, 1 H), 7.10–7.13 (m, 1 H) and 7.17–7.22 (m, 2 H); m/z (FD) 258 (M⁺, 100%).

5-tert-Butyl-6,7-benzoylbicyclo[3.2.0]heptan-3,6-dien-2-one (20). To a solution of 19 (400 mg, 1.55 mmol) in dichloromethane (12 mL) was added pyridinium tribromide (545 mg, 1.71 mmol) in one portion, and the mixture was stirred at room temperature for 40 h and then poured into a mixture of benzene (100 mL) and 10% aqueous Na₂SO₄ (50 mL). The organic layer was separated, washed with brine (50 mL), dried with Na₂SO₄, and concentrated. The residue was dissolved in dry THF (12 mL) and added dropwise to a solution of trityl chloride (500 mg, 1.55 mmol) and sodium hydride (60 mg, 1.55 mmol). The mixture was stirred at 60 °C for 30 min and then evaporated. The residue and the mixture were extracted with ether (3 × 70 mL). The extracts were combined, washed with brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:9) to give 20 (0.78 g, 82%); mp 256.0886, C₁₄H₁₂OCl₂ requires 262.0891; v max (neat/cm⁻¹) 1730; δ₁₇ (300 MHz; CDCl₃) 0.91 (s, 9 H), 2.02–2.09 (m, 2 H), 2.22–2.44 (m, 2 H), 2.53–2.59 (m, 2 H), 2.80–2.86 (m, 1 H) and 3.61–3.78 (m, 4 H); m/z (FD) 266 (M⁺ + 4, 11.2%), 264 (M⁺ + 2, 63.8%) and 262 (M⁺, 100%).
The residue was subjected to chromatography on silica gel eluted with ether/hexane (1:9) followed by preparative GPC (chloroform) to give 20 (236 mg, 61%); mp 162–164 °C (hexane); (Found 256.1474, C, 19.73, H, 1.15; requires 268.1827); m/z (FD) 268 (M+). The absorption assigned to 496 (sh) and 507 (sh) nm. For 5–7 at 458 nm in EPA was estimated to be 2500 ± 500. Similarly, the rate constants for the dimerization of 6 and 7 in EPA at 0 °C were determined to be 166 ± 3 M−1 s−1 and 60 ± 12 M−1 s−1, respectively.

Attempted photochemical generation of 8 from 22. A degassed EPA solution of 22 (3.0 × 10−4 M) in a Pyrex tube was irradiated with a high pressure Hg lamp at −196 °C and the reaction was monitored by UV-vis spectroscopy. In contrast to the photolysis of 12–14 described above, development of no absorption extending to long-wavelength region characteristic of the 3,4-benzotropane system was observed, even after irradiation for 150 min. TLC analysis of the photolysate showed complete consumption of 22 together with the formation of two products: However, preparative scale photolysis of 22 (16 mg, 0.06 mmol) in EPA (50 mL) at 12 °C resulted in the formation of a complex mixture. Similar medium dependent photochemical behavior has been reported for parent 2.

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References


Measurement of the electronic absorption spectra of 5–7. A solution of precursor 12, 13 or 14 in EPA was placed in a Pyrex tube and degassed by freeze-thaw cycles. The sealed tube was immersed in liquid nitrogen in a Dewar having two parallel windows facing each other and the sample was irradiated through the window with a high pressure Hg lamp. When a solution of the precursor (3.2 × 10−4 M) in EPA was irradiated at −196 °C for 10 min, development of a new absorption assigned to 5–7 was observed. For 5: λmax 331 (sh), 353, 373, 394, 452, 473 (sh), 498 (sh) and 510 (sh) nm. For 6: λmax 331 (sh), 352 (sh), 371, 392, 445, 472 (sh), 496 (sh) and 507 (sh) nm. For 7: λmax 351, 369, 389, 453, 482 (sh), 503 (sh) and 517 (sh) nm. The absorption assigned to 5 remained unchanged for more than 10 h at −78 °C, but disappeared rapidly at 0 °C. The decay of the absorption followed second-order kinetics and the rate constant determined by monitoring the decay at 458 nm was 30 ± 6 M−1 s−1 in EPA at 0 °C. The molar absorptivity of 5–7 at 458 nm in EPA was estimated to be 2500 ± 500.