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## Cyclization of benzyne-tethered alkyllithiums: preparation of 3-substituted benzocyclobutenes and 5-substituted tetralins

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## Abstract

A five-step, one-pot preparation of isomerically pure 3-substituted benzocyclobutenes or 5-substituted tetralins in 20–40% yield from the appropriate  $\alpha$ -(2-fluorophenyl)- $\omega$ -iodoalkane, involving generation and subsequent 4or 6-*exo* cyclization of a benzyne-tethered alkyllithium, is described. © 1999 Elsevier Science Ltd. All rights reserved.

We recently reported that ring-closure of the benzyne-tethered alkyllithium generated from 2-fluoro-1-(3-iodopropyl)benzene (1), as illustrated in Scheme 1, delivers isomerically pure 4-substituted indans (2) in 60–70% yield following trapping of 4-indanyllithium with an electrophile.<sup>1</sup> While intramolecular addition of heteroatomic nucleophiles or stabilized carbanions to a tethered benzyne is a well developed synthetic procedure,<sup>2</sup> the generation and cyclization of benzyne-tethered alkyllithiums remains a largely unexplored area. For this reason, it was of interest to explore the possibility of preparing other benzofused carbocycles by extension of our methodology to 4-*exo* and 6-*exo* cyclization of benzyne-tethered alkyllithiums. Herein we report that both 3-substituted benzocyclobutenes (4) and 5-substituted tetralins (6) may be prepared, albeit in modest yield, via the five-step, one-pot sequence summarized in Scheme 1.



Scheme 1.

The  $\alpha$ -(2-fluorophenyl)- $\omega$ -iodoalkane substrates, 3 and 5, were prepared in straightforward fashion as summarized in Scheme 2.<sup>3</sup> Generation of a benzyne-tethered alkyllithium from a 2-fluorophenyl

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iodoalkane involves the three discrete steps illustrated in Scheme 1: (i) lithium-iodine exchange, (ii) *ortho*-lithiation of the resulting (2-fluorophenyl)alkyllithium, and (iii) rapid loss of LiF to give the benzyne intermediate. As noted in our initial report,<sup>1</sup> the only problematic feature of this conceptually simple approach to a benzyne-tethered alkyllithium is an obvious one: the (2-fluorophenyl)alkyllithium produced in the first step is capable of acting as the base for the subsequent *ortho*-lithiation. This potential difficulty was easily circumvented once it was realized that *t*-BuLi, rendered monomeric by addition of THF to the reaction mixture, is apparently a much better reagent for *ortho*-lithiation than is a presumably aggregated primary alkyllithium.<sup>1</sup>



Scheme 2.

The generation and cyclization of benzyne-tethered alkyllithiums was accomplished following our previously reported protocol.<sup>1</sup> Thus, addition of 3.2 equiv. of *t*-BuLi in heptane to a  $-78^{\circ}$ C solution of either **3** or **5** in *n*-pentane:Et<sub>2</sub>O (4:1 by vol.) results in rapid exchange and consumes two equiv. of *t*-BuLi. Addition of a quantity of dry THF sufficient to render the residual *t*-BuLi monomeric (ca. 0.5 mL/mmol of substrate) and removal of the cooling bath initiates the three-step cascade depicted in Scheme 1. As demonstrated by the results summarized in Table 1, addition of any of a variety of electrophiles to the reaction mixture serves to deliver isomerically pure 3-substituted benzocyclobutenes (**4**) or 5-substituted tetralins (**6**) in moderate yield.<sup>4</sup> It might be noted that, although the 4-*exo* or 6-*exo* cyclization of benzyne-

Table 1

Preparation (Scheme 1) of 3-substituted benzocyclobutenes (4) and 5-substituted tetralins (6)



a. Isolated yield of chromatographically pure product unless otherwise noted b Yield determined by GC after correction for detector response.

tethered alkyllithiums derived from 3 and 5 is less efficient in terms of yield than is 5-*exo* cyclization of a benzyne-tethered propyllithium leading to 4-substituted indans,<sup>1</sup> the benzocyclobutene (4) and tetralin (6) products (Table 1) are easily isolated by chromatography since the balance of the reaction mixtures consist mainly of unfunctionalized oligomeric material.

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- Satisfactory C and H analyses were determined for all previously unreported compounds and their spectroscopic properties were fully in accord with the assigned structures. 2-Fluoro-1-(2-iodoethyl)benzene (3): <sup>1</sup>H NMR δ 3.21 (t, *J*=7.41 Hz, 2H), 3.35 (t, *J*=7.41 Hz, 2H), 7.06 (m, 2H), 7.20 (m, 2H); <sup>13</sup>C NMR δ 3.78, 33.72, 115.48 (d, *J*=21.9 Hz), 124.08 (d, *J*=3.4 Hz), 127.37 (d, *J*=15.7 Hz), 128.67 (d, *J*=8.2 Hz), 130.69 (d, *J*=4.6 Hz), 160.89 (d, *J*=245.6 Hz); Anal. calcd for C<sub>8</sub>H<sub>8</sub>FI: C, 38.43; H, 3.22. Found: C, 38.57; H, 3.53. 2-Fluoro-1-(4-iodobutyl)benzene (5): <sup>1</sup>H NMR δ 1.72 (m, 2H), 1.87 (m, 2H), 2.67 (t, *J*=7.42 Hz, 2H), 3.20 (t, *J*=6.94 Hz, 2H), 7.03 (m, 2H), 7.17 (m, 2H); <sup>13</sup>C NMR δ 6.42, 27.85, 30.93, 32.95, 115.22 (d, *J*=22.3 Hz), 123.95 (d, *J*=3.4 Hz), 127.63 (d, *J*=8.2 Hz), 128.54 (d, *J*=16.0 Hz), 130.54 (d, *J*=2.8 Hz), 161.10 (d, *J*=244.2 Hz). Anal. calcd for C<sub>10</sub>H<sub>12</sub>FI: C, 43.19; H, 4.35. Found: C, 43.51; H, 4.66.
- 4. All of the benzocyclobutenes (4) and tetralins (6) prepared in this study (Table 1) are known compounds whose physical and spectroscopic properties are fully in accord with those reported in the literature.