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

William F. Bailey * and Sarah C. Longstaff

Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060, USA

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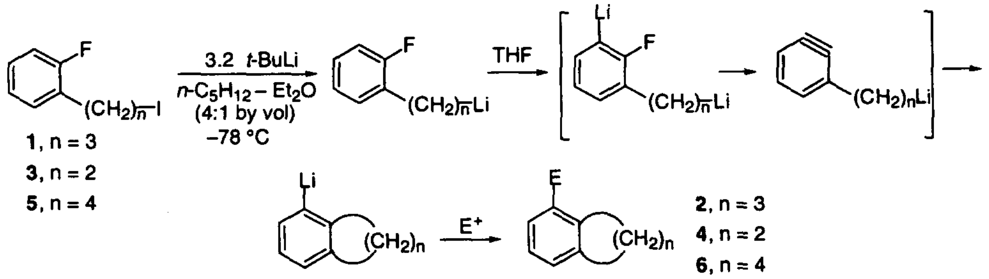
Abstract

A five-step, one-pot preparation of isomerically pure 3-substituted benzocyclobutenes or 5-substituted tetralins in 20–40% yield from the appropriate α-(2-fluorophenyl)-ω-iodoalkane, involving generation and subsequent 4- or 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.[1] While intramolecular addition of heteroatomic nucleophiles or stabilized carbanions to a tethered benzyne is a well developed synthetic procedure,[2] 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 benzo-fused 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 α-(2-fluorophenyl)-ω-iodoalkane substrates, **3** and **5**, were prepared in straightforward fashion as summarized in Scheme 2.[3] Generation of a benzyne-tethered alkyllithium from a 2-fluorophenyl

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* Corresponding author.

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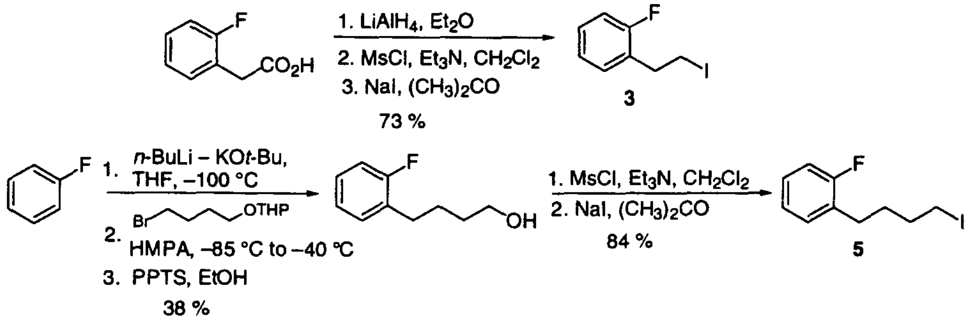
iodoalkane involves the three discrete steps illustrated in Scheme 1: (i) lithium–iodine exchange, (ii) *ortho*-lithiation of the resulting (2-fluorophenyl)alkyllithium, and (iii) rapid loss of LiF to give the benzyne intermediate. As noted in our initial report,[1] the only problematic feature of this 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.[1]

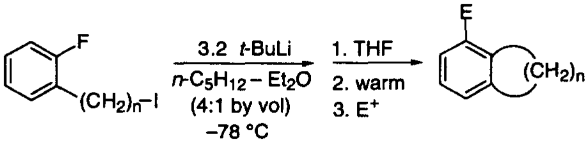


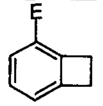
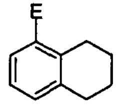
Scheme 2.

The generation and cyclization of benzyne-tethered alkyllithiums was accomplished following our previously reported protocol.[1] Thus, addition of 3.2 equiv. of *t*-BuLi in heptane to a –78°C solution of either **3** or **5** in *n*-pentane:Et_2O (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.[4] 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**)



					
E^+	E	yield,[a] %	E^+	E	yield,[a] %
CH_3OH	H	45[b]	CH_3OH	H	41[b]
$Br(CH_2)_2Br$	Br	30	DMF	CHO	35
DMF	CHO	32	$ClCO_2C_2H_5$	$CO_2C_2H_5$	30
$ClCO_2CH_3$	CO_2CH_3	21	$(CH_3)_3CCHO$	$(CH_3)_3CCH(OH)$	36

[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,[1] 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.

Acknowledgements

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2. (a) Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, *83*, 1691. (b) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *72*, 91. (c) Kessar, S. V. *Acc. Chem. Res.* **1978**, *11*, 283, and references cited therein. (d) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178. (e) Biehl, E. D.; Khanapure, S. P. *Acc. Chem. Res.* **1989**, *22*, 275, and references cited therein.
3. 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**): ^{1}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); ^{13}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_8H_8FI: C, 38.43; H, 3.22. Found: C, 38.57; H, 3.53. 2-Fluoro-1-(4-iodobutyl)benzene (**5**): ^{1}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); ^{13}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 $C_{10}H_{12}FI$: 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.