## 1,4-Pentadienyl-3-sulfonamides: Frameworks for "Disfavored" Radical Cascade Cyclizations

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## ABSTRACT



1,4-Pentadienyl-3-sulfonamides afford products including those resulting from disfavored 5-*endo-trig* reactions when subjected to radical cyclization conditions. Products resulting from pathways featuring 4-*exo-trig* cyclizations are also detected, even when the 4-*exo-trig* reaction leads to a highly strained bicyclo[3.2.0] ring system.

The outcome of radical cyclization reactions can usually be predicted by applying the rules that were announced by Baldwin<sup>1</sup> 25 years ago (and subsequently developed by Beckwith<sup>2</sup> in specific relation to radical cases). The examples in Baldwin's original papers focused especially on the disfavored nature of *5-endo-trig* reactions. *5-Endo-trig* radical cyclizations are rare,<sup>3,4</sup> and steric and electronic factors are frequently present<sup>3</sup> that help to mitigate the unfavorable

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factors. We now report a novel specific series of sulfonamides that flout the 5-*endo-trig* guideline, where there is no obvious rationalization for this behavior.

Dienes  $1^5$  were treated with tributyltin hydride and AIBN and afforded<sup>6</sup> the expected products **2**. However, the yield of **2** was very low, and further investigation revealed that a second type of product was present as a mixture of

(6) A mixture of tributyltin hydride (1.5 equiv) and AIBN (0.25 equiv) in solution in benzene was added by syringe pump over 7–12 h to the substrate (10 mM in benzene) while heating under reflux. Treatment with iodine and DBU, filtration, and chromatography afforded the products; see: Curran, D. P.; Chang, C.-T. J. Org. Chem. **1989**, *54*, 3140.

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<sup>(5)</sup> Compounds **1**, **7**, **15**, **16**, and **24** were prepared by Mitsunobu coupling of the corresponding 1,4-dien-3-ols with the appropriate sulfonamide. In the cases of **7**, **15**, **16**, and **24** the desired product was contaminated by the isomeric 2,4-dienyl-1-sulfonamides. The latter isomers were removed by Diels-Alder reaction with 4-phenyl-1,3,4-triazoline-2,5-dione followed by chromatographic separation to leave the pure desired products.



diastereoisomers. This structure was assigned as 6, and this was confirmed by selective crystallization of one of the isomers  $6^*$  and subsequent single-crystal X-ray structure determination.

Two pathways were considered for formation of cyclopentene 6: (a) 5-endo-trig cyclization of intermediate 3 to afford the cyclopropylcarbinyl radical 4, which following fragmentation and hydrogen atom abstraction afforded 6, or (b) a fragmentation-cyclization pathway via 5. Although the fragmentation to a vinyl radical, 5, would not be favored on energetic grounds, slow progress through an unfavorable equilibrium might, in principle, afford 5, which should then cyclize in a favorable 5-exo-trig mode onto the activated alkene to yield the observed product 6 following hydrogen atom abstraction. To distinguish between the two possible mechanisms and to explore the scope of the reaction, substrate 7a was prepared and subjected to radical cyclization. This afforded both the product expected from 5-exotrig cyclization followed by reductive termination, 8a (as a mixture of isomers) and the 5-endo product 9a, the latter being the *predominant* product. Intriguingly, it also afforded the indole 10 (20%). This product can be rationalized by a second cyclization (4-exo-trig) of **11 cis** to afford the highly strained bicyclo[3.2.0] intermediate **12**. (To our knowledge, this is the first example of a radical cyclization to form the four-membered ring of a bicyclo[3.2.0] system). Fragmentation of this radical, **12**, produces the somewhat stabilized indolinyl intermediate **13**, which yields **14** by loss of the sulfinyl radical and then tautomerizes to indole **10**. Variation of the sulfonamide group as in **7b**,**c** altered the relative yield of the products: "normal" product **8b**, (12%), **8c** (0%), **5**-*endo* product **9b**, (29%), **9c** (25%), and indole **10** (24% from **7b**, 31% from **7c**).

The formation of products **9** in these reactions cannot occur by a fragmentation route as discussed for the substrate (**1**) and clearly demonstrates that the normally disfavored 5-*endotrig* pathway is in operation. To test the generality of the reaction, the seven- and eight-membered ring dienes **15** and **16** were then prepared. Cyclization of **15** led to the tricycle **17** (50%). If tetracyclic radicals **19** and **20** were formed, their reversal to **18** was too rapid to permit reduction by tributyltin hydride. By contrast, however, the eight-membered substrate **16** afforded not only the simple tricyclic product **21** (20%) but also the two products resulting from transannular cyclization, **22** (37%) and the indole **23** (10%). This con-



jugated product must arise by tautomerism of the initially formed isomer.

All of the examples reported above feature an aryl ring; to see if this was a prerequisite for the 5-*endo* cyclization, chloroamide (**24**) was prepared and treated with tributyltin hydride under the normal conditions. This afforded the expected monocyclic pyrrolidine product (**25**, 48%) as the principal product. However, the bicyclic amide (**26**, 15%), resulting from 5-*endo* cyclization, was also formed.

It is clear that the dienesulfonamide substrates examined in this study constitute a class of compounds that undergo normally disfavored radical cyclizations with unusual ease. The examples studied in this communication all feature unactivated alkenes and use tributyltin hydride, which features a relatively weak Sn-H bond. Extension of the studies to substrates with activated radical acceptor sites and alternative radical-chain carriers is currently under investigation.

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**Supporting Information Available:** NMR spectra for all products and crystallographic information files (in CIF format) for compound **6**\*. This material is available free of charge via the Internet at http://pubs.acs.org.

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